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UNC CANCER CARE

Racial Disparities in Endometrial Cancer: Molecular Studies of Black Women with Endometrial Cancer

UNC TREND
PROGRAM ON TRANSLATIONAL RESEARCH IN ENDOMETRIAL CANCER DISPARITIES

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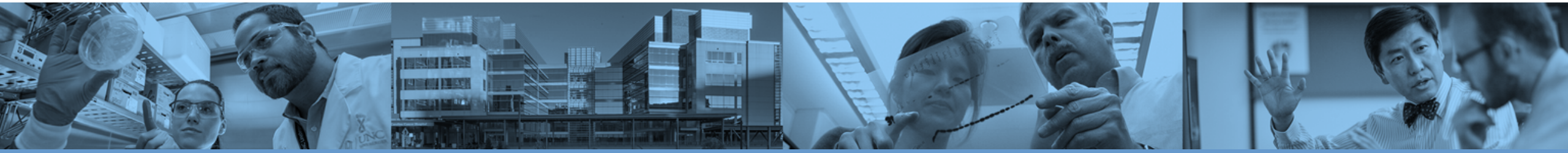


Disclosures

- Merck – collaborative grants
- Oncoceutics/Chimerix – drugs for pre-clinical studies, collaborative grants
- Cardero/Sphaera – drugs for pre-clinical studies, collaborative grants
- Eisai – consulting
- Genentech - drug for pre-clinical studies, collaborative grants
- None relevant to talk today.

Endometrial Cancer (EC) and Obesity

- 4th most common cancer among women in the U.S.[1]
- Increasing in frequency and mortality due to the obesity epidemic.[2]
- In 2022, 65,690 new cases of endometrial cancer will be diagnosed in the US. [1]
- Average age of diagnosis is 60 years old.[1]
- Obesity, diabetes and insulin resistance are well-known risk factors associated with a higher risk of developing and dying from endometrial cancer.[3]

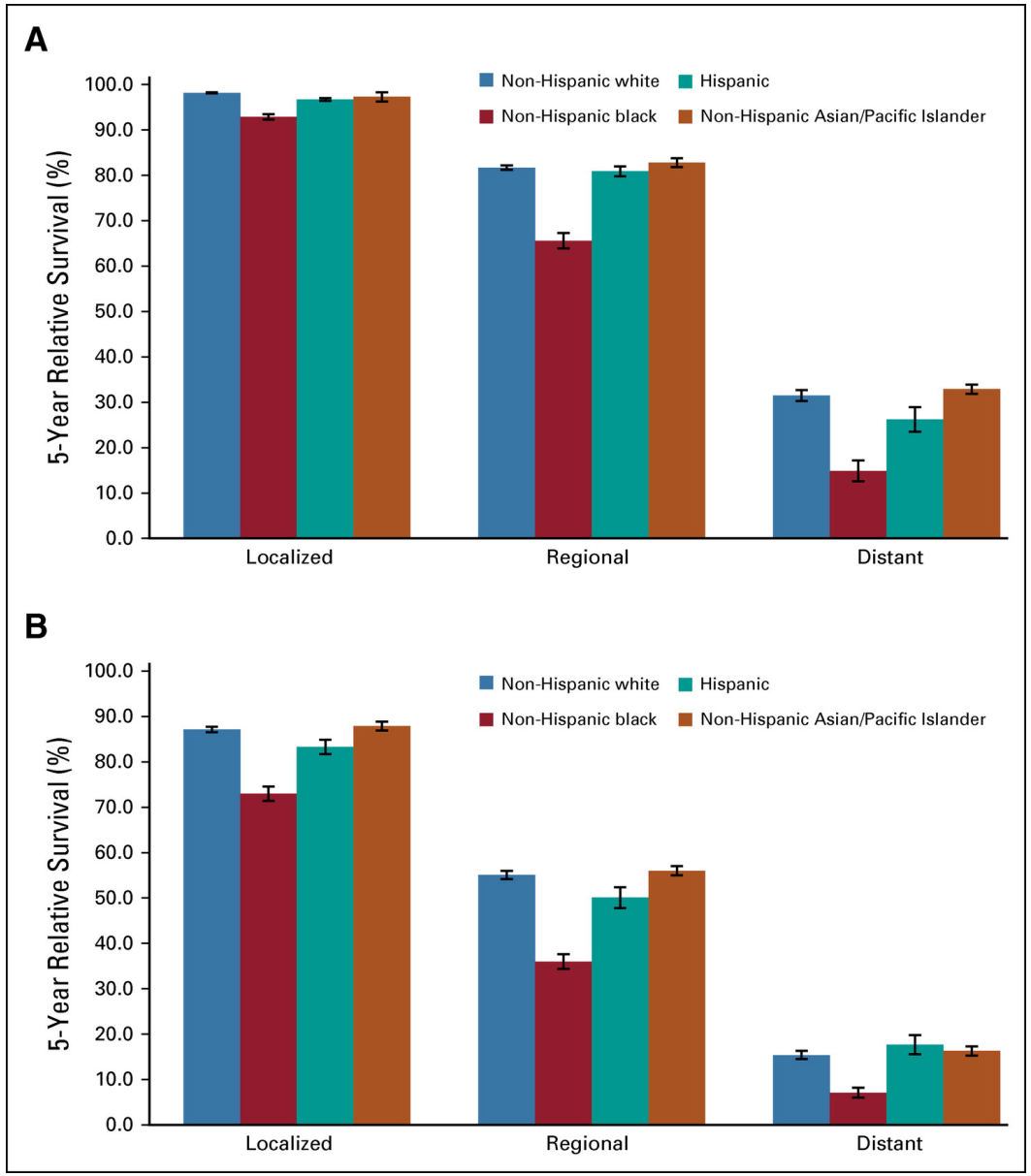
[1] Seigel et al. Cancer Statistics. 2022
[2] Annual Report to the Nation on the Status of Cancer, 2019
[3] Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. Int J Gynecol Cancer. 2007;17(2):441-6.

Endometrial Cancer and Race

- **Black women suffer a higher mortality from endometrial cancer (EC) than White women.[4]**
- **Incidence rates are increasing 3-fold for Blacks compared to Whites (2.2% annual increase vs 0.7%) and mortality rates are twice as high (8.5 vs 4.4/100,000).**
- **The overall 5-year survival is 81%; yet 5-year survival among Black women is 62% vs. 83% for White women.**
- **Blacks have the lowest survival rates, regardless of stage or histologic subtype, and mortality rates are increasing disproportionately by race (2.2% annual increase for Blacks, 1.6% for Whites).**

[4]Cote ML, Ruterbusch JJ, Olson SH, Lu K, Ali-Fehmi R. The Growing Burden of Endometrial Cancer: A Major Racial Disparity Affecting Black Women. *Cancer Epidemiol Biomarkers Prev*. 2015;24(9):1407-1415

- **Black EC patients do worse than all other races**
  - True for localized, regional and distant disease.
  - True for Type 1 and Type 2 disease.
- **Type 2 cancers behave more aggressively and disproportionately affect Black women.**



Type 1: Endometrioid

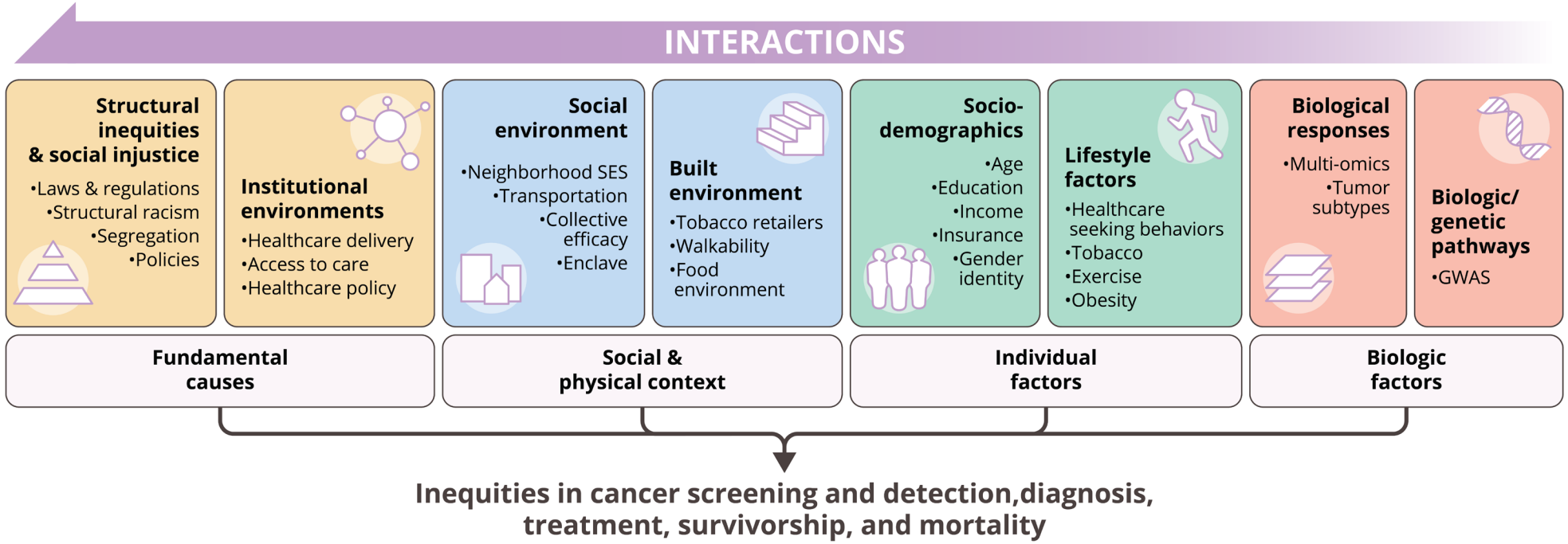
Type 2: Non-Endometrioid

Clarke et. al., JCO May 2019

Why are there racial disparities for endometrial cancer?

- **Access to equitable care**
- **Social determinants of health**
- **Host environment and response to treatment**

- **Higher risk of more lethal histologic and molecular subtypes**
- **Higher rates of obesity and/or diabetes**
- **Other unknown biological factors?**



The “Cell to Society” model created by the UNC Lineberger Cancer Center, adapted from Warnecke *et al. Am J Public Health* 2008

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Endometrial Cancer

- **Early stage disease, endometriod histology – good prognosis with surgery +/- radiation**
- **Early stage disease, non-endometrioid histology – high recurrence rate, treat with surgery, chemotherapy +/-radiation**
- **Advanced endometrial cancer – poor overall survival with triple modality treatment**
  - **Stage 3: 40-50%**
  - **Stage 4: 5-20%**
- **Recurrent endometrial cancer – overall survival of 14-15 months**

Endometrial Cancer –Type 1 and 2

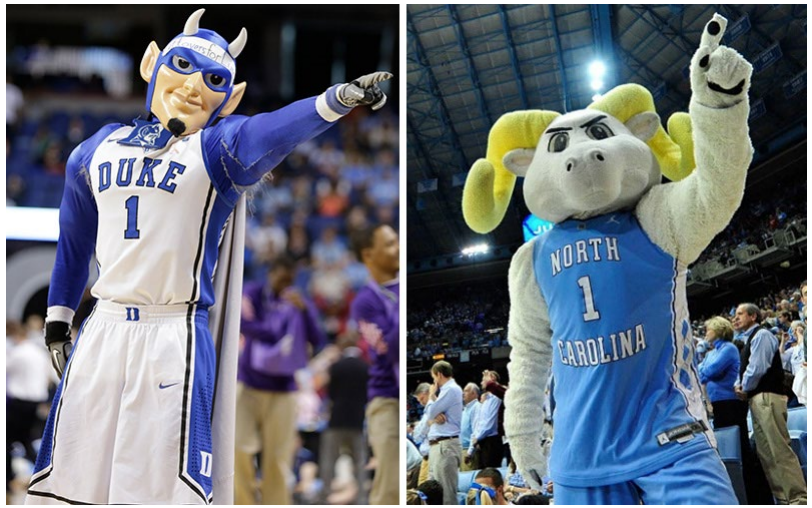
- **Type I (80%)**
  - **Endometrioid histology**
  - **Most diagnosed Stage I**
  - **High 5-year survival**
  - **Estrogen related**
  - **Associated with obesity, DM and HTN**
  - **Associated with atypical endometrial hyperplasia.**
- **Type II (20%)**
  - **Non-Endometrioid – serous, clear cell, other high risk histologies**
  - **Aggressive**
  - **Often present in advanced stage**
  - **Poorer 5-year survival**
  - **More common in Black patients**

- **Obesity and diabetes are associated with both endometrioid and non-endometroid endometrial cancers.**

Mutch, GOG Symposium, 2007

Obesity and Diabetes Rates in Type I and II Endometrial Cancers

- **Multi-institutional study of 1400 endometrial cancer patients**
- **High obesity rates in both Type I EC and Type II patients (66% versus 51%, p<0.0001).**
- **Similar rates of diabetes in Type 1 and II patients (25% versus 23%, p=0.69).**
- **Obesity rates – 75% Black vs 58% of White (p<0.0001)**
- **Black EC patients twice as likely to have diabetes (p<0.001)**
- **Obesity linked to chemoresistance due to metabolic dysfunction.**



Ko et al., Gynecologic Oncology, 2014; 133: 28-32.

Genetic Alterations by Subtype

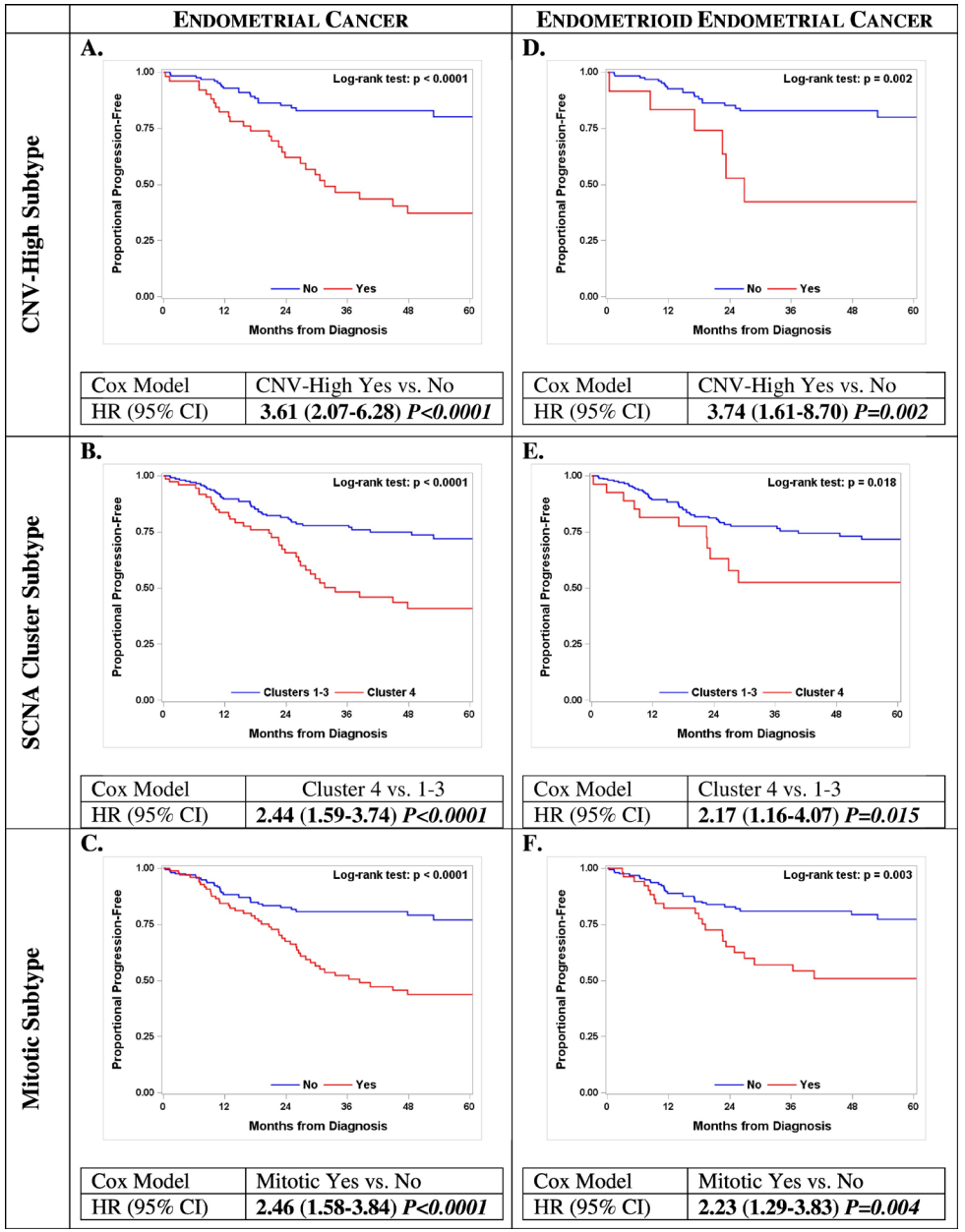
- **Endometriod (Type 1)**
  - Microsatellite instability
  - PTEN deletions/mutations
  - PIK3CA mutations/amplification
  - PIK3R1/PIK3R2 mutations
  - Activation of K-ras
  - ARID1A mutations
  - β-catenin mutations
- **Non-Endometrioid (Type 2)**
  - p53 mutations
  - Overexpression of HER-2/neu
  - p16 inactivation
  - PIK3CA mutations/amplification
  - E-cadherin alterations

The Cancer Genome Atlas Project

	POLE (Ultramutated)	MSI (Hypermutated)	COPY-NUMBER LOW	COPY-NUMBER HIGH (Serous-like)
Copy Number Alterations	Low	Low	Low	High
MSI/MLH 1 Methylation	Mixed MSI high, low, stable	MSI High	MSI stable	MSI stable
Mutation Rate	Very High (232 x 104 Mutations/Mb)	High (18 x 104 Mutations/Mb)	Low (2.09 x 104 Mutations/Mb)	Low (2.3 x 104 Mutations/Mb)
Genomic Profile	POLE (100%) PTEN (94%) P1K3CA (71%) P1K3R1 (65%) FBXW7 (82%) AR1D1A (76%) KRAS (53%) AR1D5b (47%) PD1/PD-L1 Overexpression	PTEN (88%) RPL22 (32%) KRAS (35%) P1K3CA (54%) P1K3R1 (40%) AR1D1A (37%) PD1/PD-L1 Overexpression	PTEN (77%) CTNNB1 (52%) P1K3CA (53%) P1K3R1 (33%) AR1D1A (42%) FGFR2 (10.9%)	TP53 (92%) PPP2R1A (22%) FBXW7 (22%) P1K3CA (47%) PTEN (11%) FGFR Amplifications & mutations (7%) HER2 amplified 25%
Histology	Endometrioid	Endometrioid	Endometrioid	Serous, Endometrioid, and Mixed
Grade	Grades 1-3	Grades 1-3	Grades 1-2	Grade 3

- Overlap between Type 1 and 2
- The POLE, MSI and CNL clusters were composed mostly of endometrioid ECs
- Serous and 25% of endometrioid ECs were found in the CNH
- CNH has 3 fold worse PFS than other subtypes

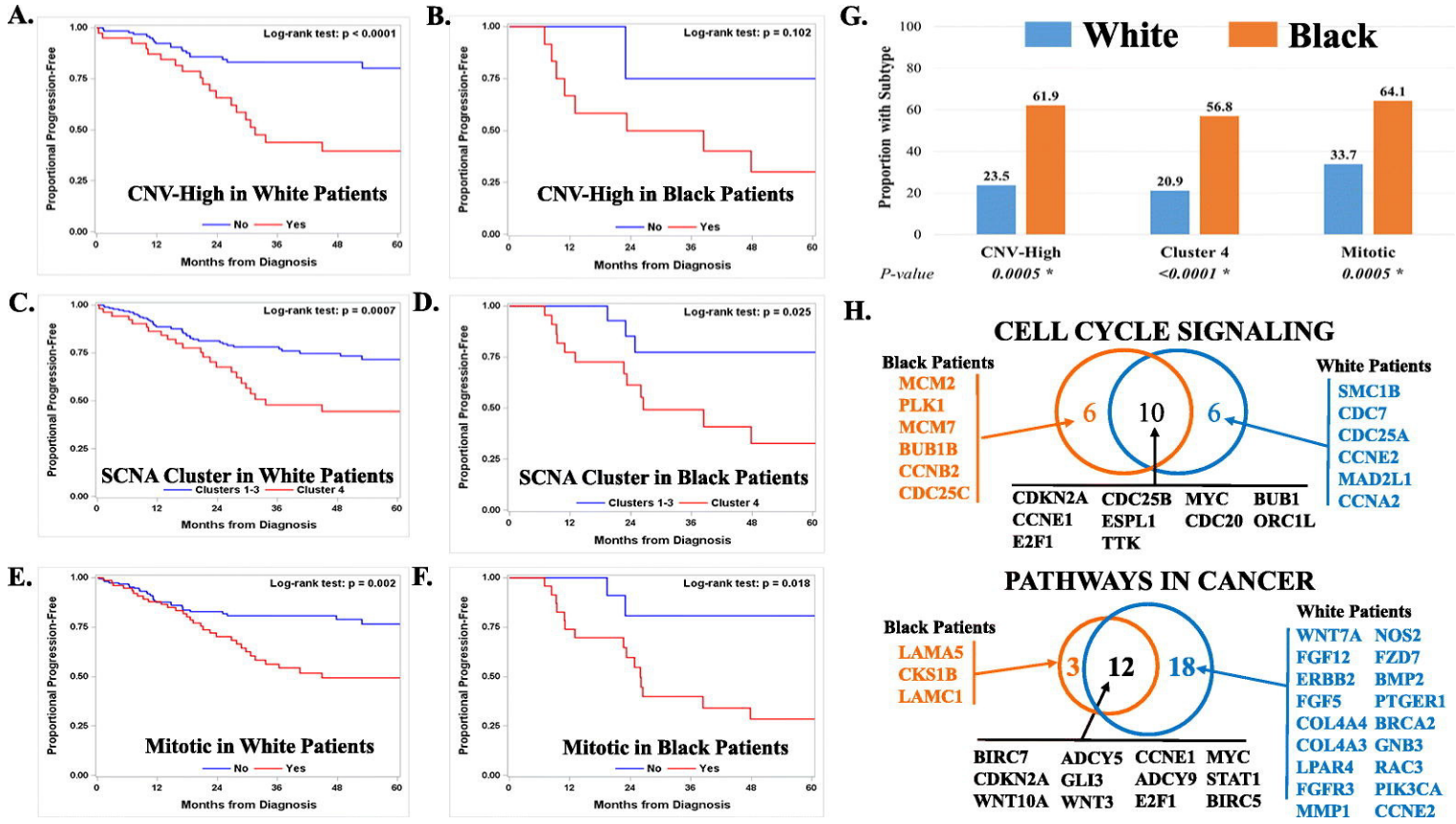
Kandoth et. al. Nature. 2013;497(7447):67-73.



- **TCGA identified several aggressive molecular subtypes in EC**
- **Copy number variant high/CNH (27%) vs POLE, MSI, CNL**
- **Somatic copy number alteration (SCNA) cluster subtype 4 (26%) vs SCNA clusters 1, 2 and 3**
- **Mitotic subtype (RNAseq) (37%) vs Immunoreactive, Hormonal**
- **14% of ECs in TCGA were from Black women (46 cases)**

Kandoth et. al. Nature. 2013;497(7447):67-73.
Dubil et. al., Gynecol Oncol. 2018;149(1):106-16.

Racial Disparities in Molecular Subtypes of EC – TCGA



- **CNH, SCNA cluster subtype 4 and mitotic subtype all more common in Black vs White Women**
- **CNH subtype – 62% of Blacks versus 24% of Whites**
- **Worse PFS for Black vs White women for each of these subtypes**
- **Race associated enrichment in cell signaling pathways.**

Kandoth et. al. Nature. 2013;497(7447):67-73.
Dubil et. al., Gynecol Oncol. 2018;149(1):106-16.

UNCseq – Endometrial Cancer Cohort

- **Black vs White patients had a higher BMI (41 vs 34), more grade 3 (52% vs 36%) and non-endometrioid (48% vs 22%) ECs, more often presented at an advanced stage (33% vs 25%) and had a greater risk of recurrence (30% vs 18%).**
- **Higher incidence of p53 mutations (47.1% vs 19.3%) in ECs from Blacks vs Whites.**
- **Higher mutation rate of PIK3CA in White versus Black serous cases.**

Modified TCGA classification	Non-Hispanic Black % (# of cases)	Non-Hispanic White % (# of cases)
POLE (ultramutated)	5.9% (3)	6.9% (19)
MSI (hypermutated)	21.6% (11)	25.5% (70)
TP53 mutation present	47.1% (24)	19.3% (53)
TP53 mutation absent	25.5% (13)	48.2% (132)
Total cases	51	274

Challenges in Cancer Disparities Research in Endometrial Cancer

- **Lack of prospective population-based epidemiologic studies detailing histologic and molecular subtype with race, obesity and co-morbid treatments, access and receipt of NCCN recommended treatment and follow-up care.**
- **Small representative numbers of EC samples from Black women in large scale molecular profiling studies such as TCGA (46 Black cases, 291 White cases; Nature. 2013;497(7447):67-73).**
- **Limited understanding of the impact of obesity and its related co-morbidities as modulators of EC progression and treatment efficacy in Black women**

https://unclineberger.org/cecs/

CAROLINA ENDOMETRIAL CANCER STUDY

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Carolina Endometrial Cancer Study (CECS)

- **NC population-based cohort – opened in February 2021**
  - 100 counties, rapid case ascertainment of all endometrial cancers thru all hospitals
  - Oversample Black women
  - 370 cases enrolled per year (170 Black, 170 White)
  - About 530 (243 Black) with baseline interview & tumor data in 1.5 years
  - About 1,000 (462 Black) with baseline interview & tumor data in 3 years – 10X the number in TCGA

CAROLINA
ENDOMETRIAL
CANCER STUDY

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Carolina Endometrial Cancer Study (CECS) – Data Collection

- ***Baseline and Follow-up* (12 and 24 months) telephone interviews**
  - Information on obesity, weight change, sociodemographic factors, racism, medical history, physical activity, family history, hormone use, access to care, financial impact, quality of life
- **Medical Records and Outcome Assessment**
  - Acquisition and abstraction of medical records related to diagnosis and treatment. Ascertain recurrence and vital status.
- **Biospecimen collection**
  - Acquisition of FFPE tumor blocks
- **Molecular Subtyping**
  - NGS (1400 gene panel), RNA sequencing, IHC

CAROLINA ENDOMETRIAL CANCER STUDY

NRG Oncology/Gynecologic Oncology Group 210 Study

- **Endometrial cancer recurrence according to race and ethnicity.**
- **GOG 210:**
  - September 2003 to December 2011
  - 62 institutions
  - > 6,000 women enrolled prior to surgery
- **Tumor Characteristics and Outcome Assessment**
- **Questionnaires**
  - Demographics – age, race, annual income, highest level of education
  - Endometrial cancer risk factors – height, weight, reproductive factors, diabetes, smoking, OCP use, HRT use, tamoxifen, history of breast cancer

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Felix et. al., Int. J. Cancer, 2018, 142, 1102-1115

NRG Oncology/Gynecologic Oncology Group 210 Study

- **4,698 endometrial cancer patients**
  - 3,199 White
  - 532 Black
  - 232 Hispanic
- **Black endometrial cancer patients were more likely to be:**
  - Obese
  - Multi-parous
  - History of diabetes
  - Non-users of HRT
  - More aggressive tumor features – advanced stage and type 2 histologies
  - Adjuvant treatment more common

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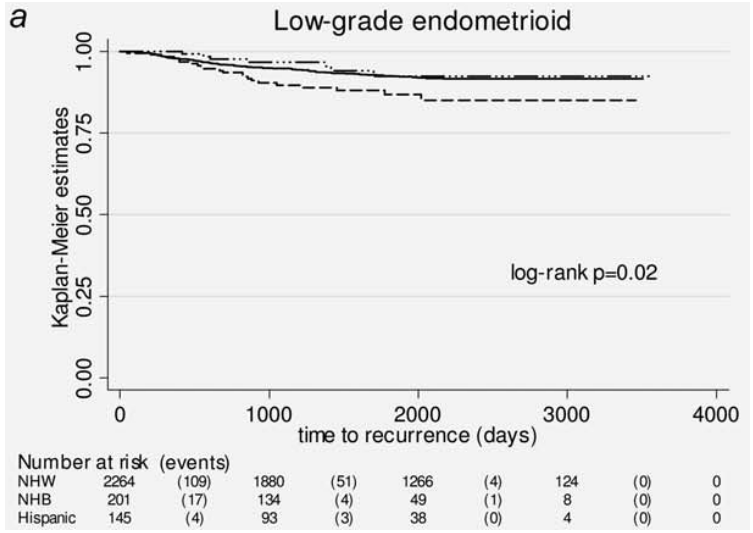
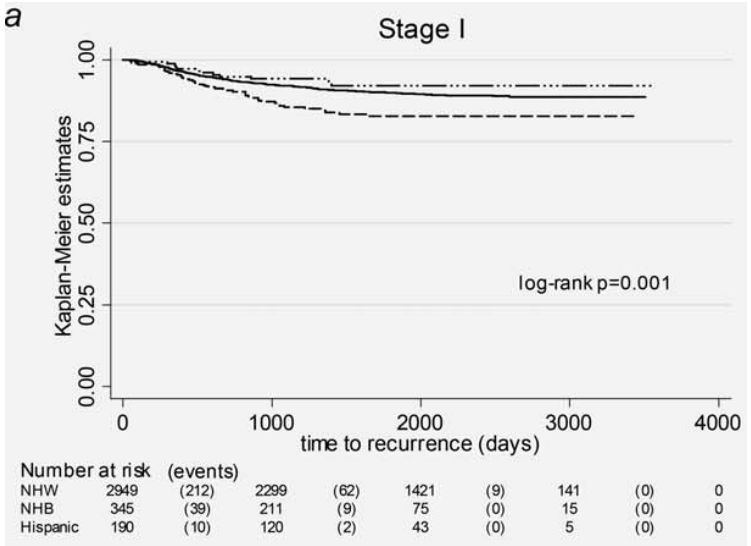
Felix et. al., Int. J. Cancer, 2018, 142, 1102-1115

NRG Oncology/Gynecologic Oncology Group 210 Study

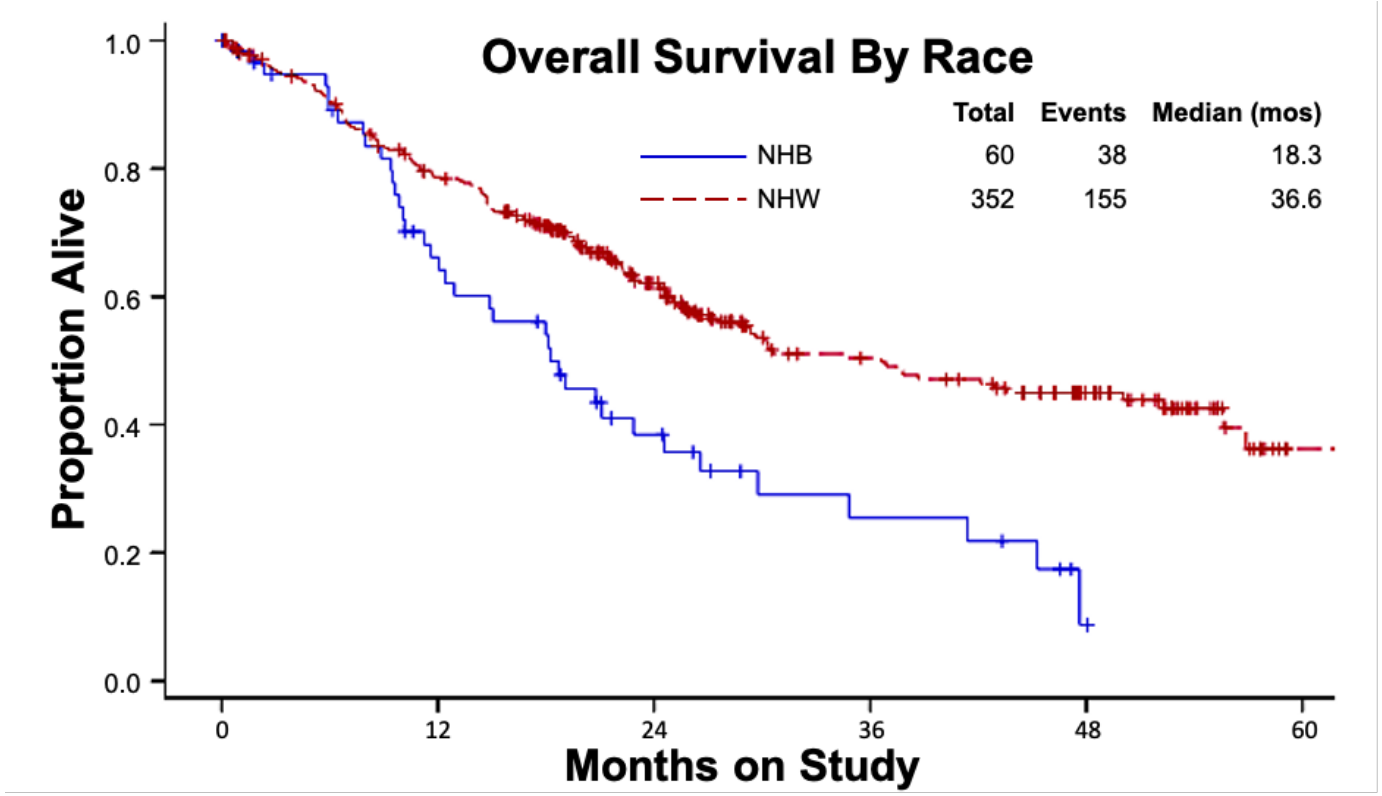




- **Black women had a higher recurrence risk overall, particularly among low grade (HR 2.06, 95% CI = 1.3-3.27) and low stage (HR 1.57, 95% CI = 1.21-3.10) tumors.**
  - Not related to tumor characteristics, SES or treatment received.
- **Conclusion: Other racial differences in tumor biology or patient characteristics should be explore.**

Felix et. al., Int. J. Cancer, 2018, 142, 1102-1115

GOG286B: Randomized Phase 2/3 Trial of Metformin vs placebo + paclitaxel/carboplatin in advanced and recurrent EC



- **Black race was associated with worse PFS than White race (HR = 1.5 95%; CI 1.098– 2.024) and worse OS than White race (HR = 2.03 95%; CI 1.429 – 2.890).**
- **Response rate also differed – 64% overall for White women, 43% for Black women.**
- **Obesity rates differed – 64% of Black women were obese *vs* 48% of White women.**

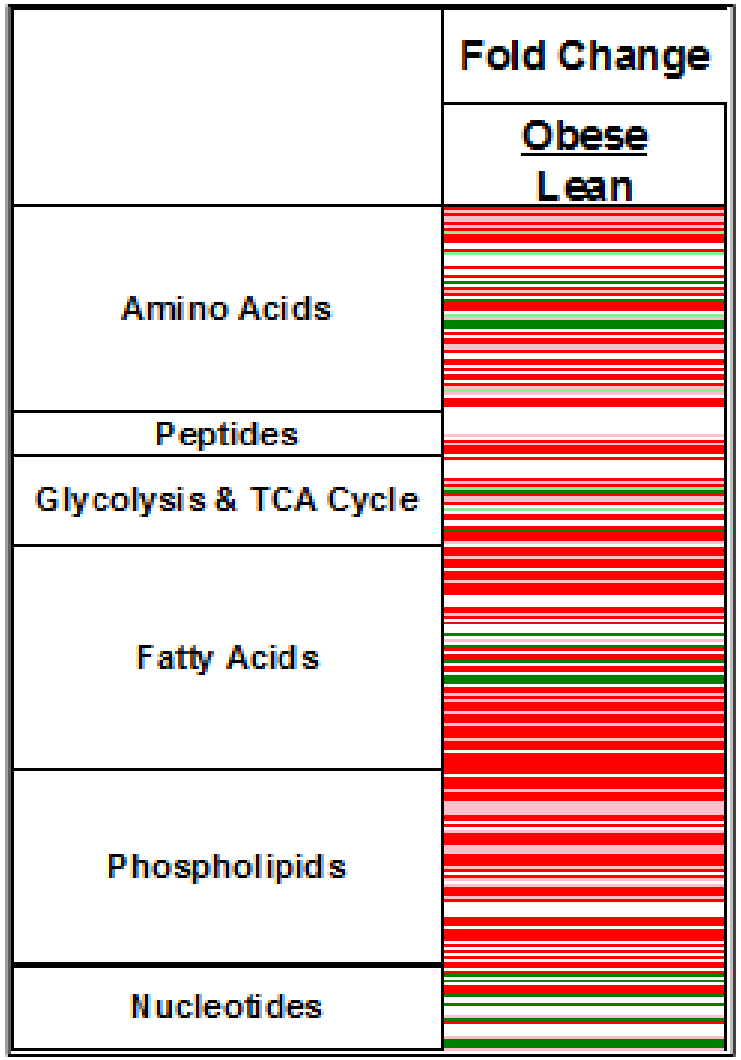
Annual Meeting of the Society of Gynecologic Oncology, April 2020

Racially-diverse PDX Models

- **Paucity of racially and molecularly defined mouse models as tools to study this disease.**
- **Racially and genomically-diverse patient-derived xenograft models of EC**
- **Obesity and microbiome studies planned.**

PDX EC Model	Race	Histology	Grade	Stage	Genomics
EC419	White	Endometrioid	2	1	*CTNNB1*, *FGFR2*, *PTEN* mutations
EC164	Black	Endometrioid	1	1	*PIK3CA*, *p53* and *ARIDIA* mutations High TMB
U190549	White	Serous	3	1	Pending
U190572	Black	Clear Cell	3	4B	Pending
U190441	Black	Endometrioid	2	3C1	Pending
U190669	White	Endometrioid	2	2	Pending
U190739	White	Carcinosarcoma	3	3C1	Pending
U190806	White	Endometrioid	2	1	MSI high

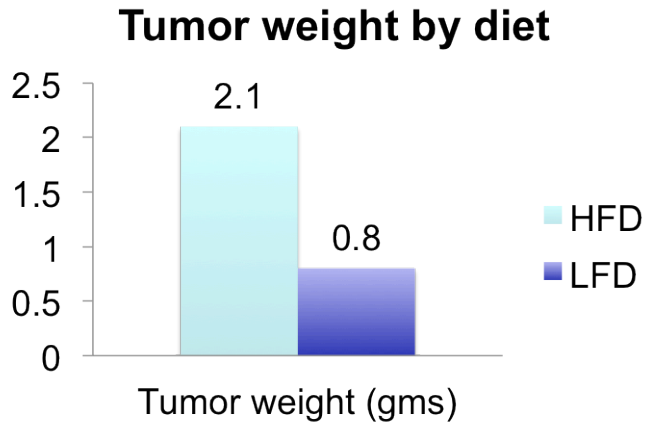
Obesity and the *Lkb1$^{fl/fl}$/p53$^{fl/fl}$* Mouse Model



INCREASE

DECREASE

- ***Lkb1$^{fl/fl}$p53$^{fl/fl}$*** **endometrioid EC mouse model – diet-induced obesity leads to more aggressive tumor behavior.**
- **Differences in obese and lean endometrial tumors:**
  - **Lipid, protein and glucose biosynthesis and bacterial metabolites related to the microbiome.**



Guo H, Kong W, Zhang L, Han J, Clark LH, Yin Y, Fang Z, Sun W, Wang J, Gilliam TP, Lee D, Makowski L, Zhou C, Bae-Jump VL. Reversal of obesity-driven aggressiveness of endometrial cancer by metformin Am J Cancer Res. 2019 Oct 1;9(10):2170-2193.

Overall Summary

- **Endometrial cancer harbors one of the worse cancer disparities for Black women than any other cancer.**
- **More aggressive molecular/genomic subtypes seems to drive this disparity in part.**
- **Why do Black women develop these aggressive molecular subtypes of endometrial cancer? Is obesity a potential driver of these more aggressive molecular subtypes?**
- **Critical to addressing this disparity is to define the molecular alterations in the ECs of Black women in the context of other biologic and non-biologic factors that may drive more aggressive behavior of EC or lead to worse outcomes – Carolina Endometrial Cancer Study**
- **Equally important is the identification of other modifiable, race-driven factors that contribute to disparate outcomes in Black EC patients**
  - **Uterine/gut microbiome?**
  - **Obesity-driven pathways – insulin/IGF-1 and Wnt/beta-catenin pathways**

Thank you!

COLLABORATORS & LAB:

- Chunxiao Zhou, MD, PhD
- Wendy Brewster, MD, PhD
- Tope Keku, PhD
- Jason Merker, MD, PhD
- Russel Broaddus, MD, PhD
- Andrew Olshan, PhD
- Buddy Weissman, PhD
- Joel Parker, PhD
- Xiaming Tan, PhD
- Weida Gong, PhD

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- American Cancer Society (ACS)
- Lineberger Comprehensive Cancer Center

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The Becky Black Memorial Fund to Fight Endometrial Cancer

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