Endometrial Cancer

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QBIO 490

Review Paper:
Endometrial cancer - Crosbie et al., 2022

Endometrial Cancer: A Review

3% - lifetime risk

- Largely sourced from **genomic** data.
- **Most common** gynecological cancer in high-income countries
- Incidence is rising globally (up 132% in last 30 years)
- **6th most common** cancer among women
- 2020 - 417,000 diagnoses
- *USA - **blacks are more likely to develop tumors over whites***

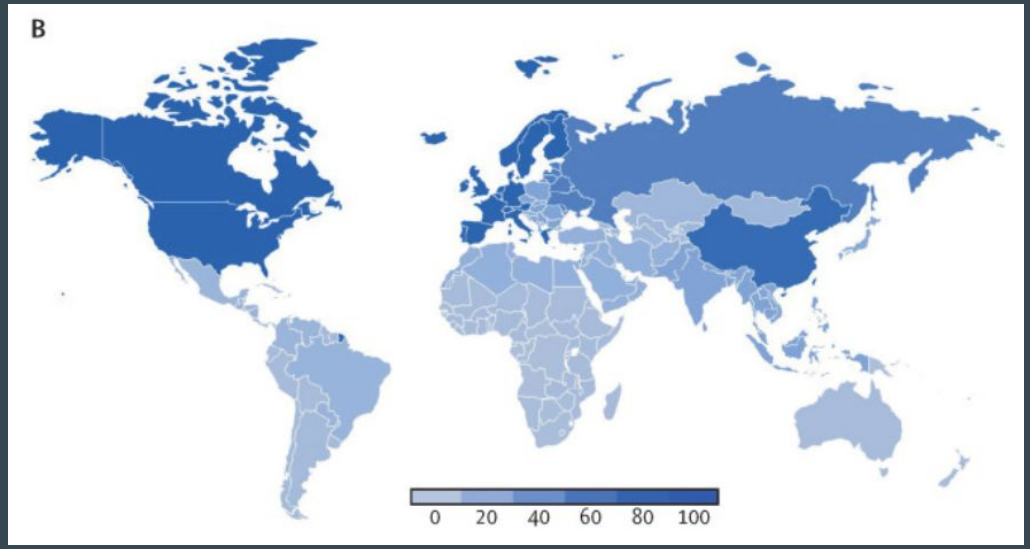

Figure 1B. Age-standardized incidence rate of endometrial cancer 2019 (100 000 population) per GBD region. *Crosbie et al., 2022.*

How do we spot endometrial cancer?

- “It’s complicated”
- Postmenopausal bleeding - **probability of cancer increases with age**
- Diagnosis requires tissue exam
- **EM thickness >= 5 mm indicates potential for cancer**

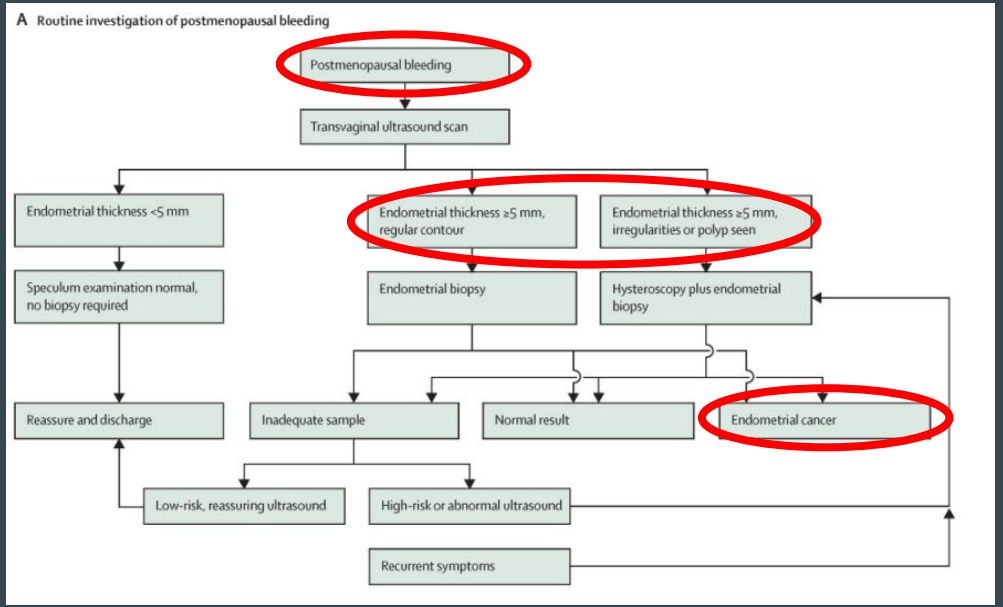

Figure 2A. Current diagnostic pathways for endometrial cancer. Crosbie et al., 2022.

Risk Factors

- Risk increases with **AGE** and **BMI** - cancer with the **strongest** link with obesity
  - BMI > 40: 10-15% chance of cancer ~ lung cancer in smokers
- Obesity -> high CRP, IL-6, TNF-alpha -> endometrial formation +
- Estrogen - EM growth, progesterone - EM in check
  - Post-menopause - progesterone deficiency

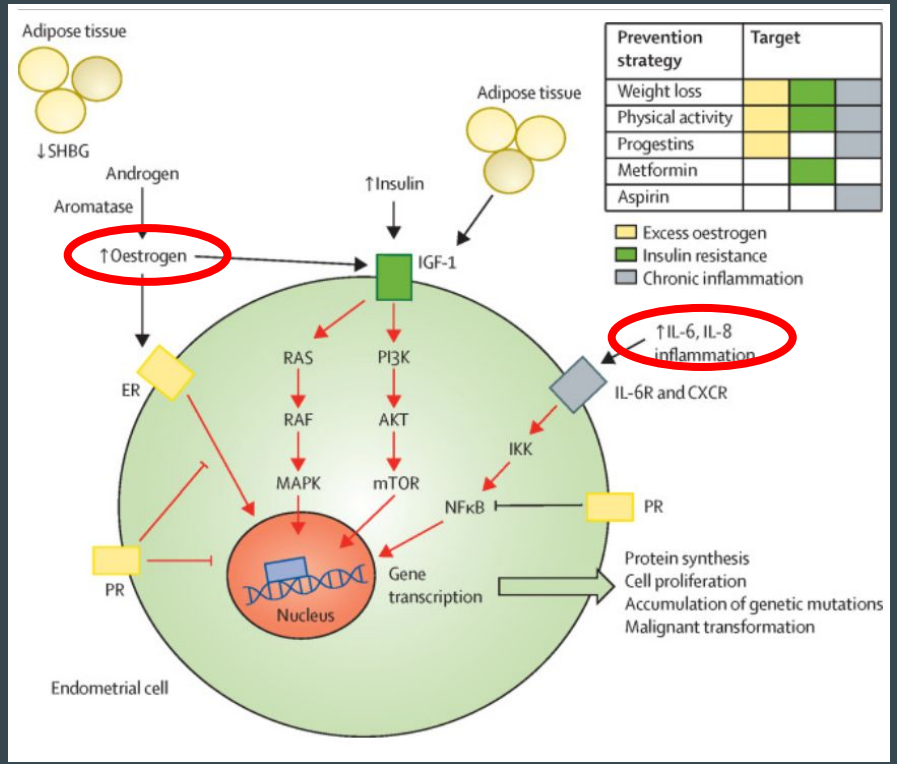

Figure 3. Obesity-associated endometrial cancer: pathways to carcinogenesis and targets for prevention. Crosbie et al., 2022.

Surgery and Treatment

- Current mainstay of treatment: **total hysterectomy + bilateral salpingo-oophorectomy**
- Minimally invasive surgery shown to have non-inferior outcomes. Preferred whenever possible
- Fertility-sparing treatment? Currently *not very great*
  - Oncological recurrence ~35% after treatment
  - Pregnancy prospects ~27%

- **Weight loss leads to both less cardiovascular disease and increased endometrial cancer survival rate**

Research Paper:
Analysis of endometrial carcinoma TCGA reveals differences in DNA methylation in tumors from Black and White women - Asif et al., 2023

Introduction

- Racial disparities
  - Tumor subtypes
  - Mortality rates
- Social determinants of health
  - Impacts on epigenetic alterations, such as **DNA methylation**
- Epigenetic modifications contribute to endometrial carcinogenesis
  - Global hypomethylation
  - Hypermethylation at CpGs in promoter regions
  - Result: **oncogene activation, tumor suppressor inhibition, genomic instability**

Gap in knowledge/hypothesis

Given that there are significant r**acial disparities** in endometrial carcinoma, and the relationship between social determinants of health and epigenetic alterations, could there be ***epigenetic*** differences in endometrial cancer between Black and White women?

Methods

- -Omics: Epigenomics and Transcriptomics
- Downloaded endometrial carcinoma methylation and clinical data from TCGA
  - 46 normal tissues and 439 tumor samples
- Parsed by race, leaving 393 samples
  - 294 White samples, 99 Black samples

1. Differentially methylated CpGs were identified using Limma package in R
2. Differentially methylated regions were identified with DMRcate
3. Survival analysis generated with survival R package
4. Correlation analysis between changes in methylation and gene expression
5. Enrichment analysis

Results

1. DMC's Analysis -

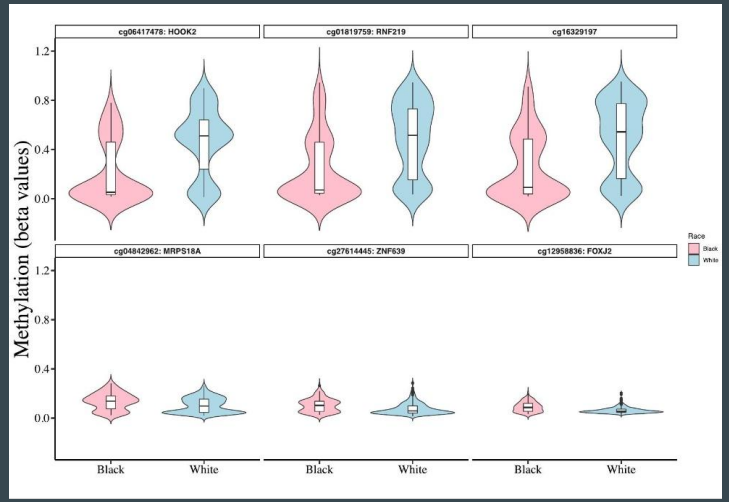

Fig 1A. Volcano plot for differentially methylated CpGs (DMCs) in tumors from White vs Black patients. *Crosbie et al., 2022*

2. DMC's Analysis -

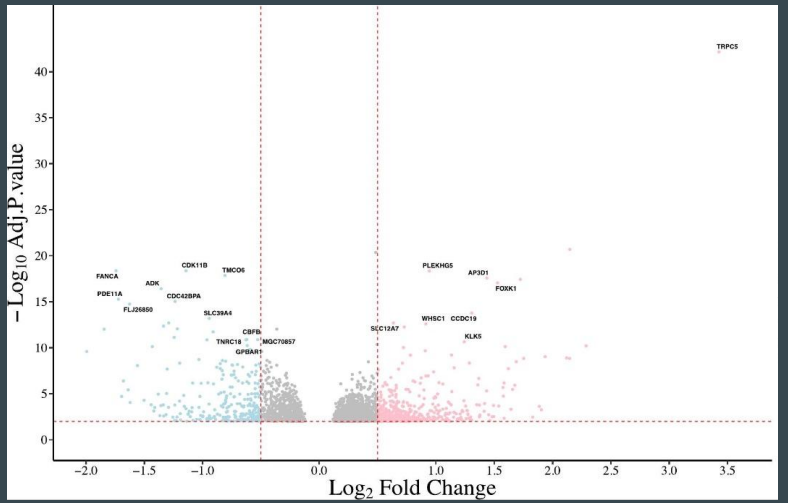

Fig 1B. Violin plot of six significant differentiated methylated CpGs (DMCs) between White and Black tumors. *Crosbie et al., 2022*

Results Contin.

3. Visualization of DMR using UCSC Genome Browser

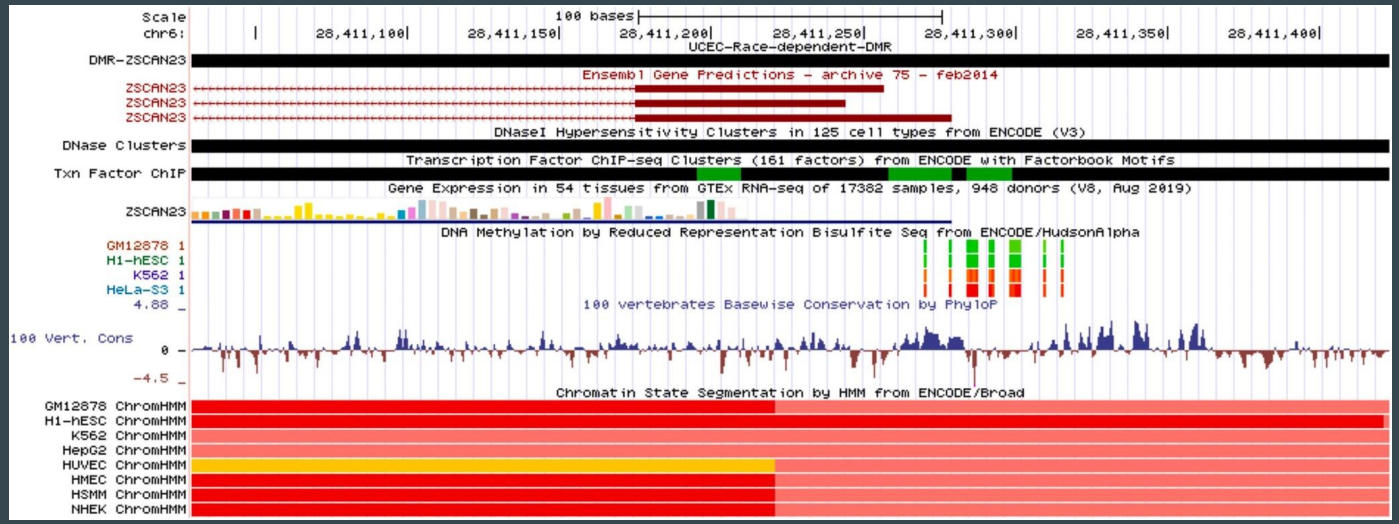

Fig 2. Visualization of DMR using UCSC Genome Browser. *Crosbie et al., 2022*

Discussion

1. Gene promoter hyper/hypomethylation is key in cancer studies
2. Linked with racial disparities in cancer incidence and mortality rounds out the epigenetic regulation of cancer-associated genes
3. Selected Genes—in insulin signaling pathway—demonstrated twice as hypervariable in Black than White tumor samples

Questions/Future Directions

1. What factors and processes are contributing to these differences in methylation between Black and White women with endometrial carcinoma?
    - Future in vitro studies could help answer this question
2. How can the discovery of differential methylation in Black and White endometrial carcinoma patients contribute to the development of new methods of diagnosis or therapeutics?
3. The review paper has shown that age and BMI impact likelihood for cancer. Is there a significant socioeconomic difference which contributes to different cancer incidence rates between Blacks and Whites in the U.S.?

Works Cited

Asif, H., Foley, G., Simon, M., Roque, D., & Kim, J. J. (2023). Analysis of endometrial carcinoma TCGA reveals differences in DNA methylation in tumors from Black and White women. Gynecologic Oncology, 170, 1-10. https://doi.org/10.1016/j.ygyno.2022.12.011.

Crosbie, E. J., Kitson, S. J., McAlpine, J. N., Mukhopadhyay, A., Powell, M. E., & Singh, N. (2022). Endometrial cancer. *The Lancet*, *399*(10333), 1412-1428.