Biological Determinants of Kidney Cancer Health Disparities

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Kidney Cancer Health Disparities: Incidence

Kidney cancer is a top ten leading cause of cancer. African Americans (AAs) have a higher incidence than European Americans (EAs).

National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, 2020
Kidney Cancer Health Disparities: Survival

5-year relative survival rates are >93%; depends on several factors (e.g. SEER stage). AAs have lower survival at regional and distant SEER stages.

National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, 2020
Renal Cell Carcinoma (RCC) is the most common type of kidney cancer, with clear cell RCC (ccRCC) being the most common histology in AAs.

de Lartigue J, OncLive, 2016; Olshan AF, Cancer Medicine, 2013
The three common RCC histologies are characterized by distinct molecular profiles.

**Clear Cell RCC**
- Increased ribose metabolism pathway mRNA expression associated with poor survival
- Increased immune signature

**Chromophobe RCC**
- Identification of metabolically divergent (MD-) ChRCCs associated with extremely poor survival

**Type 1 Papillary RCC**
- \(PBRM1\) mutations associated with poor survival
- Increased mRNA signature for RNA splicing and cilium genes

**Type 2 Papillary RCC**
- Increased expression of the glycolysis, ribose metabolism, and Krebs cycle genes in comparison to Type 1 PRCC

**Renal Cell Carcinoma (RCC)**
- Increased DNA hypermethylation and \(CDKN2A\) alterations associate with poor prognosis in all RCC subtypes
- Increased Th2 immune signature within each RCC subtype associates with poor survival

**Subtype** | **Most Common Mutations** | **Drugs/ Targets**
--- | --- | ---
**Clear Cell** | \(VHL, PBRM1, SETD2, KDM5C, PTEN, BAP1, MTOR, and TP53\) | Bevacizumab (VEGF)
- Pazopanib (VEGFRs 1-3, PDGFR, FGFR, c-KIT)
- Sunitinib (VEGFRs 1-3, c-KIT, PDGFR)
- Sorafenib (VEGFRs 1-2, PDGFR, c-KIT, RAF)
- Axitinib (VEGFRs 1-3, PDGFR)
- Everolimus (mTOR)
- Temsirolimus (mTOR)

**Papillary Type 1** | \(MET\) | Forotinib (MET/VEGFR2)

**Papillary Type 2** | \(CDKN2A, SETD2, TFE3\) fusions, NRF2-ARE pathway | Anti-VEGF agents

**Chromophobe** | \(TP53, PTEN, FAAH2, PDHB, PDX-DG1, ZNF765\) | mTOR inhibitors

Ricketts CJ, Cell Reports, 2018; de Larügue J, OncLive, 2016
Genetic Mutation Differences By Race in ccRCC Patients

Recent work has identified population-specific differences in ccRCC tumor biology from AAs compared with EAs. Both VHL mutation frequencies and types differ.

Krishnan B, JAMA Oncology, 2016
Tumor Biology Differences By Race in ccRCC Patients

AAs are more likely to have ccB, the more aggressive ccRCC tumor subtype.

Are there other genetic and tumor biology differences that contribute to kidney cancer health disparities in AAs?

Krishnan B, JAMA Oncology, 2016
**Hypothesis, Specific Aims, and Experimental Design**

**Hypothesis:** AA and EA ccRCC patients have population-specific somatic copy number variations and differences in tumor biology.

**Specific Aim 1:** To identify population-specific SCNV profiles between African Americans and European Americans with ccRCC at the genome, chromosome, and gene levels of taxonomy.

**Discovery Cohort:**
- AA: $n = 55$
- EA: $n = 458$

**Validation Cohort:**
- AA: $n = 30$
- EA: $n = 30$
Hypothesis, Specific Aims, and Experimental Design

**Hypothesis:** AA and EA ccRCC patients have population-specific somatic copy number variations and differences in tumor biology.

**Specific Aim 2:** To determine if population-specific SCNV profiles correlate with relevant kidney cancer gene expression and clinical outcomes.
Reference Genome

1000 Genomes Project
The 1000 Genomes Project is a database that provides information about human genetic variation from 26 populations around the globe.

### Table 1. Demographic Characteristic of 1000 Genomes Project Study Participants Serving as the Reference Genome

<table>
<thead>
<tr>
<th>Sex (%)</th>
<th>AA (ASW, n = 99)</th>
<th>EA (CEU, n = 182)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>53 (54)</td>
<td>93 (51)</td>
<td>0.7</td>
</tr>
<tr>
<td>Male</td>
<td>46 (46)</td>
<td>89 (49)</td>
<td></td>
</tr>
</tbody>
</table>
Patient Cohorts

Discovery Cohort: TCGA
Validation Cohort: Geisinger/CHTN
Table 2. Clinical and Demographic Characteristics of Clear Cell Renal Cell Carcinoma Patients in the TCGA Cohort

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 55)</th>
<th>EA (n = 458)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) *</td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.9</td>
<td>60.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37-81</td>
<td>26-90</td>
<td></td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>28 (51)</td>
<td>153 (33)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (49)</td>
<td>305 (67)</td>
<td></td>
</tr>
<tr>
<td>Stage (%) +</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>I</td>
<td>38 (69)</td>
<td>217 (48)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (9)</td>
<td>49 (11)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6 (11)</td>
<td>112 (24)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5 (9)</td>
<td>78 (17)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>2 (0)</td>
<td></td>
</tr>
<tr>
<td>Grade (%) +</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>4 (7)</td>
<td>10 (2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25 (46)</td>
<td>188 (41)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21 (38)</td>
<td>181 (40)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (4)</td>
<td>74 (16)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (5)</td>
<td>5 (1)</td>
<td></td>
</tr>
<tr>
<td>Vital Status (%) ^&amp;</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Dead</td>
<td>11 (20)</td>
<td>159 (35)</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>44 (80)</td>
<td>296 (65)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3 (0)</td>
<td></td>
</tr>
</tbody>
</table>

^Fisher's exact test, * Chi square test, # t test
* unknown patients removed from significance testing
<table>
<thead>
<tr>
<th></th>
<th>West African Ancestry</th>
<th></th>
<th>European Ancestry</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Self-Reported</td>
<td>Self-Reported</td>
<td>Self-Reported</td>
<td>Self-Reported</td>
</tr>
<tr>
<td></td>
<td>African Americans</td>
<td>European Americans</td>
<td>African Americans</td>
<td>European Americans</td>
</tr>
<tr>
<td></td>
<td>(n = 55)</td>
<td>(n = 458)</td>
<td>(n = 55)</td>
<td>(n = 458)</td>
</tr>
<tr>
<td>Min %</td>
<td>0.22</td>
<td>0.1</td>
<td>3.41</td>
<td>33.59</td>
</tr>
<tr>
<td>Max %</td>
<td>93.39</td>
<td>60.28</td>
<td>97.91</td>
<td>99.41</td>
</tr>
<tr>
<td>Mean %</td>
<td>73.72</td>
<td>1.53</td>
<td>23.35</td>
<td>94.68</td>
</tr>
<tr>
<td>Median %</td>
<td>78.63</td>
<td>0.49</td>
<td>19.14</td>
<td>97.73</td>
</tr>
<tr>
<td>0-20% Ancestry # (%)</td>
<td>2 (3.6)</td>
<td>455 (99.4)</td>
<td>32 (58.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>21-40% Ancestry # (%)</td>
<td>0 (0)</td>
<td>2 (.4)</td>
<td>16 (29.1)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>41-60% Ancestry # (%)</td>
<td>7 (12.7)</td>
<td>1 (0.2)</td>
<td>6 (10.9)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>61-80% Ancestry # (%)</td>
<td>25 (45.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>81-100% Ancestry # (%)</td>
<td>21 (38.2)</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td>433 (94.5)</td>
</tr>
</tbody>
</table>
Genome-wide Analyses

Do genome-wide SCNV profiles in tumor tissues from African Americans and European Americans with clear cell RCC vary?
Do genome-wide SCNV profiles in tumor tissues from African Americans and European Americans with clear cell RCC vary?

Population-specific genome-wide SCNV profiles displayed subtle global variation.
Chromosomal Analyses

Do chromosomal SCNV profiles in tumor tissues from African Americans and European Americans with clear cell RCC vary?
Do chromosomal **amplification** profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?

- **All**
  - 188,752 chromosomal regions with SCNVs
  - 48,864 chromosomal regions differ by race \((P + \text{FDR} < 0.05)\)

- **AAs**
  - 741 amplified regions \((\geq 3 \text{ copies, } P + \text{FDR} < 0.05)\)
  - Every chromosome except 20, X, and Y, 121 cytobands, and 141 genes

- **EAs**
  - 868 amplified regions \((\geq 3 \text{ copies, } P + \text{FDR} < 0.05)\)
  - Every chromosome except 20, 21, X, and Y, 100 cytobands, and 216 genes

- **There are several regional population-specific amplifications.**
  - 38 in AAs and 17 in EAs
Do chromosomal amplification profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?
Do chromosomal **deletion** profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?

- **All**
  - 188,752 chromosomal regions with SCNVs
  - 48,864 chromosomal regions differ by race \((P + \text{FDR} < 0.05)\)

- **AAs**
  - 38,806 deleted regions \((\leq 1 \text{ copy}, P + \text{FDR} < 0.05)\)
  - Every chromosome except 9, 16, 18, 20, 21, 22, and X, 42 cytobands, and 45 genes

- **EAs**
  - 38,802 deleted regions \((\leq 1 \text{ copy}, P + \text{FDR} < 0.05)\)
  - Every chromosome except 8, 9, 14, 18, 20, 21, 22, and X, 40 cytobands, and 42 genes

- **There are several regional population-specific deletions.**
  - 15 in AAs and 12 in EAs
Do chromosomal deletion profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?
Gene Analyses

Do gene SCNV profiles in tumor tissues from African Americans and European Americans with clear cell RCC vary?
Do gene amplification and deletion profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?

- **AAs**
  - GSTM1: Amplified SCNV
  - GSTM2: Amplified SCNV

- **EAs**
  - GSTM1: Deleted SCNV
  - GSTM2: Deleted SCNV

- There are population-specific SCNV and gene expression profiles.
  - More amplifications and greater expression in AAs
Do gene amplification and deletion profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?

- In European populations, GSTM1-null genotypes (i.e. deletions) have been associated with:
  - Increased risk of ccRCC development
    - OR (95% CI), P value: 1.88 (1.08–3.26), 0.02
  - Favorable overall survival
  - Due to a GSTM1:ASK1 protein-protein interaction

- This clinical correlation has not been explored in AAs with ccRCC.
  - Perform overall and disease free survival analysis based on genotype

Coric VM, Urologic Oncology, 2017; Huang W, Scientific Reports, 2015
Do gene **amplification** and **deletion** profiles vary in tumor tissues from African Americans and European Americans with clear cell RCC?

- In EA (CEU) and African (YRI) populations, **GSTM1** genotypes (CC, CT, and TT) have been associated with CNV status:
  - Greater C regions indicate a germline CNV
  - YRI → More C → Segmental Duplication
  - CEU → Less C → Segmental Deletion

- **GSTM1** genotypes vary in frequency by genetic ancestry, which may drive gene expression (**eQTL**).
  - An eQTL is a locus that explains genetic variance of a gene expression phenotype. It involves a direct association test between genotype and gene expression levels typically measured in tens or hundreds of individuals.

- **eQTL** analyses stratified by genetic ancestry have not been explored in AAs with ccRCC.

Huang RS, Human Molecular Genetics, 2009
Future Directions

1) Explore the relationship between \textit{GSTM1} genotypes in AA ccRCC patients and:
   • Survival
   • CNV status
   • Gene expression
   • Genetic ancestry

2) Perform tumor biology analyses by race and ancestry
   • Loss of heterozygosity
   • Chromothriipsis

3) Validate findings in a separate cohort
Population-specific gene amplifications driven by genetic ancestry may identify novel therapeutic targets and prognostic factors, which can improve kidney cancer precision medicine.
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