Genomic and ancestry-associated determinants of survival in gynecologic cancers

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Background

- Survival outcomes for gynecologic cancers vary across populations. However, the genomic features and other factors that contribute to these differences are poorly defined.
- We leveraged a large, real-world dataset to examine how genetic ancestry, tumor genomics, and histology are associated with overall survival (OS) in endometrial (EC), ovarian (OC), and cervical cancer (CC).

Methods

- This retrospective analysis used integrated data from Natera's proprietary de-identified Real-World Database, which includes whole-exome sequencing (WES), electronic health records, mortality records (Veritas Technologies, LLC), and medical claims from the hybrid data ecosystem CHRONOS™ (Forian, Inc).[1]
- Tumor and germline WES data were obtained as part of the workflow for a personalized, tumor-informed mPCR-NGS circulating-tumor DNA assay (Signatera™, Natera, Inc.).
- Somatic variants were called using Mutect2 and VarScan2,[2,3] and microsatellite instability (MSI) status by msisensor2.[4]
- Ancestry was inferred by EthSeq[5] and classified into predefined groups: African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS).
- Cancer histologies were extracted from clinical records using natural language processing. OS associations were evaluated using Cox proportional hazards models.

Table 1. Patient and tumor characteristics

Characteristic	Endometrial (N=3949)	Ovarian (N=3501)	Cervical (N=1060)
Age at dx, median (range) years	69 (24–100)	65 (13–97)	54 (15–91)
Genetic ancestry, N (%)			
AFR	602 (15)	296 (8)	130 (12)
AMR	446 (11)	447 (13)	251 (24)
EAS	147 (4)	141 (4)	64 (6)
EUR	2681 (68)	2543 (73)	602 (57)
SAS	69 (2)	73 (2)	12 (1)
Unknown	4 (<1)	1 (<1)	1 (<1)
Stage, N (%)			
I	1027 (26)	524 (15)	158 (15)
II	307 (8)	331 (9)	151 (14)
III	1263 (32)	1345 (38)	358 (34)
IV	952 (24)	1022 (29)	293 (28)
Unknown	400 (10)	279 (8)	100 (9)
MSI status, N (%)			
MSI-High	602 (15)	46 (1)	8 (<1)
MSS	2510 (64)	2690 (77)	833 (79)
Missing	837 (21)	765 (22)	219 (21)

Abbreviations: dx, diagnosis; MSI, microsatellite instability; MSS, microsatellite stable

Multi-modal real-world data on 8,500 patients with gynecologic cancer reveals influence of ancestry, somatic variants, and other factors on survival.

Figure 1. Genes frequently harboring tumor variants in gynecologic cancers

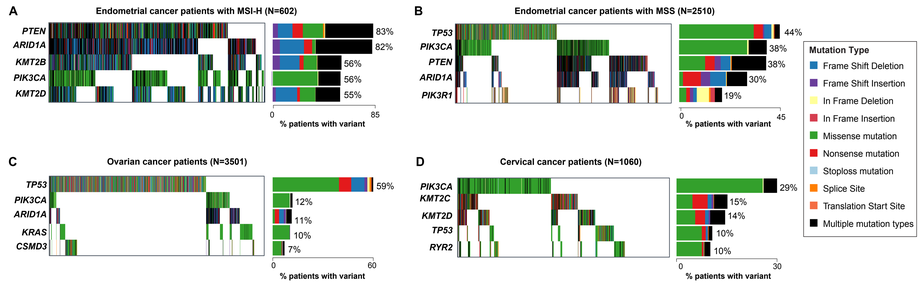

Figure 1. The genes that most frequently harbored a tumor variant were examined in: **A.** MSI-High EC, **B.** MSS EC, **C.** OC, and **D.** CC. In each panel, the colored vertical lines in the left plot represents a tumor variant in the indicated gene, and each column of vertical lines represents a patient. The horizontal bar graph on the right indicates the percentage of patients with the tumor variant among patients tested for that gene. The type of DNA change (i.e., mutation) for each variant is indicated by color.

Figure 2. Outcomes for endometrial cancer patients by tumor and patient characteristics

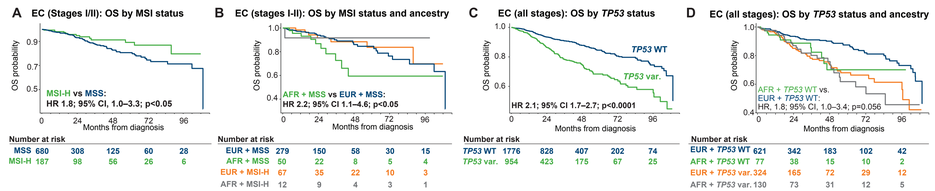

Figure 2. The impacts of tumor characteristics and genetic ancestry on EC outcomes were investigated using Kaplan-Meier estimates. **A.** Among EC patients with early-stage disease (stage I–II), those with MSS tumors had significantly worse OS than those with MSI-high tumors (HR 1.8; 95% CI 1.0–3.3; p<0.05). **B.** When stratified by ancestry, early-stage AFR patients with MSS tumors had 2x worse OS compared to EUR patients who also had MSS tumors (HR 2.2; 95%CI 1.1–4.6; p<0.05). **C.** Among all stages of EC, those with somatic *TP53* variants are high-risk and had 2x worse OS than those without (HR 2.1; 95% CI 1.7–2.7; p<0.0001). **D.** When further stratified by ancestry, patients with wildtype (WT) *TP53* and AFR ancestry trended toward worse OS than EUR patients with WT *TP53* (HR 1.8; 95% CI 1.0–3.4; p=0.056). Among individuals with *TP53* variants, there was no OS difference between those with AFR ancestry and those with EUR ancestry (HR 1.04 ; 95% CI 0.66-1.62; p=0.876).

Figure 3. Outcomes for ovarian and cervical cancer patients by tumor and patient characteristics

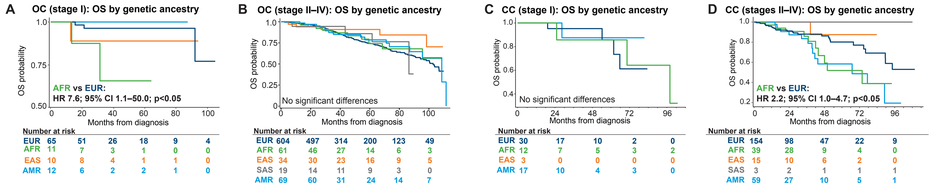

Figure 3. Kaplan-Meier estimates of OS by ancestry were also conducted in OC and CC patients. **A.** OC stage I patients with AFR ancestry had significantly worse OS than those with EUR ancestry (HR 7.6; 95% CI 1.1-50.0; p<0.05). **B.** Among OC stages II–IV, no ancestry-based differences in OS were significant for all pair-wise comparisons against EUR patients. **C.** In CC, OS was not significantly different across ancestries among individuals with stage I disease. **D.** However, among stage II–IV CC patients, AFR ancestry was associated with worse survival compared to EUR ancestry (HR 2.2, HR 1.0–4.7; p<0.05).

Figure 4. Genetic ancestry and tumor histology in gynecologic cancers

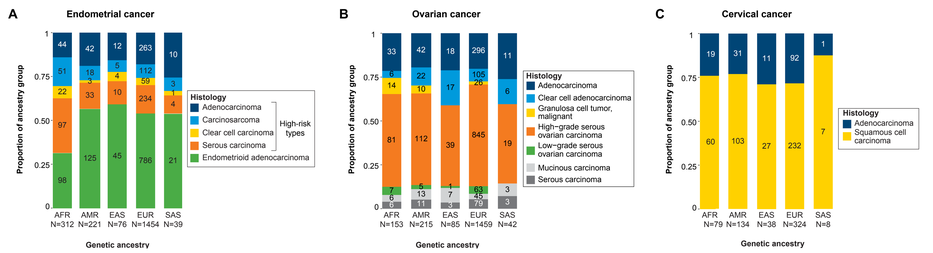

Figure 4. The distribution of histologies was examined across genetic ancestries. In all panels, the counts (numbers in colored boxes) and proportion (height of colored boxes) of individuals with a histology are shown. **A.** In EC, high-risk histologies were more common in those with AFR ancestry (68.6%; 214/312) compared to those with EUR ancestry (45.9%; 668/1454; Pearson's χ^2 with Yates' continuity correction p-value<0.0001). **B.** In OC, those with AFR, AMR, and EAS genetic ancestry had significantly different proportions of histologies compared to those with EUR genetic ancestry, with a greater proportion of EAS patients having clear cell adenocarcinoma (20%, 17/85) compared to EUR (7.2%,105/1459; χ^2 p-value<0.0001). **C.** In CC, histologies were distributed similarly across ancestries.

Conclusions

- Different gynecologic cancers have unique tumor genomic profiles that can also vary by genome instability status.
- Across the three gynecologic cancers, patients with AFR ancestry had worse survival outcomes compared to those with EUR ancestry.
- AFR, AMR, and EAS ancestry showed distinct distributions of tumor histologies compared with EUR.
- Further study of ancestry-informed genomic and pathologic data into clinical research may reduce survival disparities in gynecologic malignancies.

References

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Disclosures

AR, VNA, SR, AA, CBS, FS, MCL, and ACE are current or former employees of Natera, Inc., and have or may hold stock or options to hold stock in the company.