Biomarker comparison of epithelial ovarian cancer and endometrial cancer by multiplatform tumor profiling

Haider. Mahdi[1], Joanne Xiu[2], Sandeep. K. Reddy[2] and Robert DeBernardo[1]
[1]The Cleveland Clinic, Cleveland, OH, [2]Caris Life Sciences, Phoenix, AZ

Abstract

Objective: TP53 has been shown as a driver mutation in epithelial ovarian (EOC) and endometrial cancers (EC). We aim to compare biomarker profiles of tumor samples in relation to TP53 mutation to look for overlapping and different treatment paradigms.

Methods: 9,193 EOC and 3,133 EC tumors were evaluated using a commercial multiplatform profiling service (CARIS Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH).

Results: TP53 was the most mutated gene in EOC (61%) and EC (43%). In both cancers compared to the TP53-mutated (TP53-MT), TP53-wild type (TP53-WT) tumors carried significantly higher mutation rates of the following genes: PTEN (EC: 41% vs. 11%; EOC: 5% vs.1.4%), PIK3CA (EC: 39% vs. 26%, EOC: 15% vs. 2.9%), KRAS (EC: 27% vs. 12% , EOC: 16% vs. 3.5%) and CTNNB1 (EC: 20% vs. 1.8%, EOC:6.3% vs. 0.3%), all p-values <0.0001, indicating higher activation of PI3K, MAPK and Wnt pathways in TP53-WT cohorts in both cancer types. Interestingly, in endometrial cancer, TP53-WT cases showed significantly higher ER (73% vs. 49%, p<0.0001); PR (61% vs. 29%, p<0.0001) and PDL1 (33% vs. 14%, p=0.0002) expression, while TP53-MT tumors showed significantly higher Her2 amplification and expression (10% vs. 1%, p<0.0001; 7% vs. 1%, p<0.0001), and these associations were absent in EOC (ER: 48% vs. 51%; PR: 19% vs. 24%, PDL1: 15% vs. 16%, Her2 FISH: 3% vs. 2%, Her2 IHC: 3% vs. 2%). In contrast, in EOC, TP53-WT tumors carried three times the cMET expression (29% vs. 9%, p<0.0001) while BRCA1/2 mutations were significantly higher in TP53-MT cases (39% vs. 23%, p=0.0003), but the difference was not seen in endometrial cancer.

Conclusion: TP53-driven EOC and EC share similarities and carry differences in molecular features. Our results reveal the genetic heterogeneity of gynecological cancers and suggest increased benefit of targeting PI3K, MAPK and Wnt pathway in TP53-WT tumors of both cancer types. While hormonal and immunomodulatory therapies may be of particular interest for TP53-WT EC, Her2 targeted therapies may benefit TP53-MT EC patients. For EOC, cMET targeted therapies and PARP inhibitors may be of particular interest for TP53-WT and TP53-MT patients, respectively.

Background

- Ovarian cancer is the most lethal gynecologic malignancy among women. Unfortunately, as there is no effective screening test, the majority of patients with ovarian cancer are diagnosed at an advanced stage.
- Endometrial cancer is the most prevalent gynecologic cancer in the United States. The majority of these patients are diagnosed at early stage and have good prognosis with a low recurrence rate.
- Ovarian and endometrial cancers encompass different histologic types with different biologic behaviors. Each histologic type has unique clinical and molecular characteristics.
- TP53 mutation is the most common molecular event in ovarian cancer especially high grade serous carcinoma and certain histologic types of endometrial carcinoma.
- It is unknown whether these two cancers share other similar molecular changes and profile. Furthermore, it is interesting to see if there are different molecular changes in patients with TP53 mutation compared to those with TP53-WT.
- We aim to compare the biomarker profiles of tumor samples in relation to TP53 mutation to look for overlapping and different treatment paradigms.

Methods

- Retrospective data analysis was done on endometrial and ovarian carcinomas that were submitted to a commercial referral diagnostic laboratory (Caris Life Sciences, Phoenix, AZ) for molecular profiling aimed to provide therapeutic information based on tumor biomarkers.
- A multiplatform approach was taken that included sequencing, immunohistochemistry (IHC) and FISH/CISH. Association studies were performed by two-tailed chi-square or Fisher Exact tests.

Results: Patient Characteristics:

	EOC		EC	
Patient Number (N)	9193		3133	
Average Age	61 (11-97)		65(20-94)	
Patient Age	**TP53 Mutated**	**TP53 Wild type**	**TP53 Mutated**	**TP53 Wild Type**
20-40	7	16	34	86
41-60	106	257	593	445
61-80	353	353	908	437
81-95	38	38	72	32
Average	66.9 yrs	63 yrs	63 yrs	59 yrs
	p<0.0001		p<0.0001	
	N(%)	N(%)	N(%)	N(%)
Specimen site	Ovary 477(30%)	322(32%)	Uterus 287(57%)	425(64%)
	peritoneum tissue 463(29%)	240(24%)	peritoneum tissue 61(12%)	40(6%)
	Colon 105(7%)	50(5%)	Lymph Nodes 26(5%)	17(3%)
	Lymph node 101(6%)	46(5%)	Connective & Soft Tissue 16(3%)	25(4%)
	Connective & Soft Tissue 85(5%)	63(6%)	Lung 15(3%)	28(4%)
	Pelvis 85(5%)	80(8%)	Ovary 13(3%)	10(2%)
	Abdomen 53(3%)	43(4%)	Abdomen 11(2%)	14(2%)
	Fallopian tube 46(3%)	13 (1.3%)	Liver 10(2%)	10(2%)
	Liver 42(3%)	28(3%)	Pelvis 10(2%)	23(3%)
	Small Intestine 40(2%)	21(2%)	Vagina 9(2%)	11(2%)
	Lung 19(1%)	14(1%)	Colon 9(2%)	10(2%)
	Other 91 (6%)	80 (8%)	42(8%)	51 (8%)
	Total N 1607	1000	509	664

Results, continued

Figure 1: TP53 mutation rates in epithelial ovarian cancer and endometrial cancer.

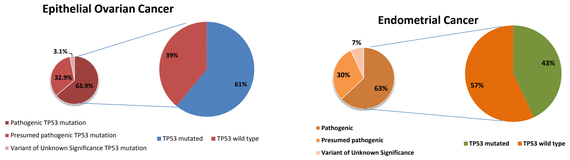


Figure 2: Biomarkers significantly different between TP53 -WT and TP53-MT cohorts in both EOC and EC. Lines indicate statistical significance.

Similarly in EOC and EC, key biomarkers on the PI3K/Akt/mTor pathway (PTEN and PIK3CA mutations), MAPK pathway (KRAS mutation) and Wnt pathway (CTNNB1 mutation) are more mutated in the TP53-WT cohort. Compared to EOC, TP53-MT EC patients exhibit higher FBXW7 mutation, potentially presenting an alternative activation mechanism of the PI3K/Akt/mTor pathway in EC, suggesting mTor inhibitors as a promising targeted therapy in TP53-MT EC despite lower mutation rates of PTEN and PIK3CA. (Jardim 2014)

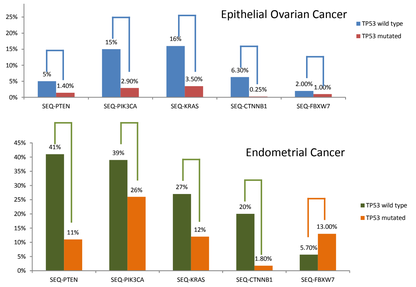
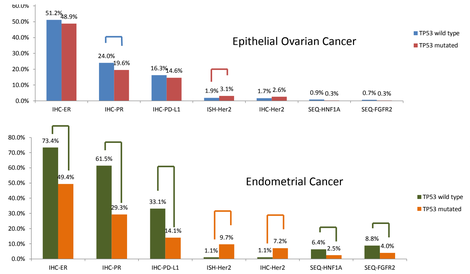


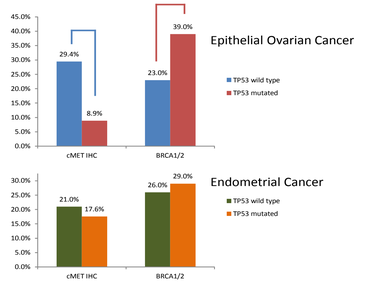
Figure 3: Biomarkers significantly different between TP53-WT and TP53-MT cohorts in EC, but not in EOC. Lines indicate statistical significance.

Overall higher hormone receptor and PDL1 expression are seen in TP53-WT tumors and the difference is more dramatic and statistically significant in EC. Interestingly, Her2 overexpression and amplification are higher in TP53-MT patients, especially in EC, presenting opportunities for Her2-targeted therapy in TP53-MT patients.



Results, continued

Figure 4: Biomarkers significantly different between TP53 wild type and TP53 mutated cohorts in EOC, but not EC. Lines indicate statistical significance.



cMET overexpression is three times higher in TP53-WT EOC patients compared to TP53-MT, potentially serving as a poor prognostic factor in patients without TP53 mutation. BRCA mutations are higher in TP53-MT EOC, consistent with high TP53 and BRCA mutations observed in serous ovarian cancer.

Conclusions

- A comparison of TP53-MT with TP53-WT tumors in both EOC and EC reveals similarities and differences in TP53-driven gynecologic cancers.
- Older patients were more likely to harbor TP53 mutations.
- Our results reveal the genetic heterogeneity of these two cancers.
- These data suggest an increased benefit of targeting PI3K, MAPK and Wnt pathways in TP53-WT tumors of both cancer types.
- Significantly higher FBXW7 mutation in TP53-MT EC cancer reveals an alternative mechanism of PI3K/Akt/mTor pathway activation.
- Hormonal and immunomodulatory therapies may be of particular interest for TP53-WT endometrial cancer. Whereas Her2-targeted therapies may benefit TP53-MT endometrial cancer patients.
- For ovarian carcinoma, cMET-targeted therapies and PARP inhibitors may be of particular interest for TP53-WT and TP53-MT patients, respectively.

References

1. Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73.
2. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011 June 30; ;474(7353):609-15.
3. Jardim, et al. FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS One. 2014 Feb 19;9(2):e89388