BRCA1 and BRCA2 mutations in 1691 epithelial ovarian tumors identify subgroups with distinct molecular characteristics

Thomas Herzog[1], Joanne Xiu[2], Ryan Bender[2], Zoran Gatalica[2], Sandeep Reddy[2]
[1]University of Cincinnati, College of Medicine, Cincinnati, USA. [2]Caris Life Sciences, Phoenix, USA.

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Abstract

Background: Increasing data has shown that ovarian cancer patients carrying BRCA1 and BRCA2 mutations, both somatic and germline, experience a survival advantage and are more sensitive to DNA damaging agents such as platinum and PARP inhibitors. We aim to identify BRCA1 and 2 mutations in various histological subtypes of epithelial ovarian cancer (EOC) tumor samples and to identify molecular differences in EOCs with or without BRCA1 or 2 mutations.

Material and Methods: A total of 1691 EOC tumors were submitted to Caris Life Sciences between April, 2014 and March, 2015 (63% serous, 5% clear cell, 4% carcinosarcoma, 3% endometrioid, 16% unannotated or carcinoma not-otherwise specified). Multiplatform molecular analysis included next generation sequencing, immunohistochemistry (IHC) of protein expression, and /or gene amplification (FISH/CISH).

Results: Deleterious BRCA1 mutations were seen in 9% (n=155) of EOC tumors [10.5% in serous, 3% in carcinosarcoma, 3% in clear cell and 2% in endometrioid]. In addition, 4.2% (72) of BRCA1 mutations characterized as presumed pathogenic (PP) or variants of unknown significance (VUS) were found. Deleterious BRCA2 mutations were seen in 5% (86) of EOC tumors [6% in serous, 6% in carcinosarcoma, 2% in endometrioid and 1% in clear cell]. In addition, 8% (136) of PP or VUS BRCA2 mutations were seen in EOC tumors. No deleterious BRCA1 and BRCA2 mutations were found to co-occur.
In the 249 EOC tumors that carried deleterious BRCA1 or 2 mutations, TP53 mutation was significantly more frequent than the BRCA-wild type tumors (83% vs. 68%, p<0.0001). BRCA-wild type EOC tumors carried significantly higher mutation rates of KRAS (10% vs. 2%, p<0.0001), PIK3CA (8% vs. 3%, p=0.003), CTNNB1 (3% vs. 1%, p=0.03) and more frequent expression of cMET (16% vs. 7%, p<0.0001).
In the 169 serous ovarian tumors with deleterious BRCA1 or 2 mutations, similar to the complete EOC cohort, a significantly higher TP53 mutation (85% vs. 67% p<0.0001), lower PIK3CA (0.6% vs. 4%, p=0.02) and KRAS mutation rates (1% vs. 7%, p=0.002) were seen compared to the BRCA-wild type serous ovarian tumors.
In the 3 clear cell ovarian tumors that carried deleterious BRCA1 or 2 mutations, 100% (3) expressed ER while in the 61 BRCA1/2 wild type clear cell tumors, only 3% (2) showed ER expression (p=0.0002)

Conclusion: Deleterious BRCA1 and 2 mutations are seen in 9% and 5% of epithelial ovarian tumors, respectively, with the highest mutation rate observed in serous histology, followed by carcinosarcoma. Oncogenic drivers including KRAS and PIK3CA are more likely to mutate in BRCA1/2-wild type EOC tumors while TP53 mutations significantly co-occur with BRCA1/2. High expression of ER in clear cell ovarian tumors with BRCA1/2 deleterious mutation suggests potential combination of hormone therapy with PARP inhibitors in this rare cancer type.

Background

While previously published clinical studies on PARP inhibitors focused on serous ovarian tumors[1], recent efforts have been made to include more histological subtypes[2]. BRCA1/2 mutations are important indicators of homologous recombination deficiency and are therefore among the most important predictor for potential responders to PARP inhibitors. We performed a systematic evaluation of BRCA1/2 mutations in a large cohort of epithelial ovarian cancer which comprised 4 histological subtypes in addition to the best studied-serous tumors. Furthermore, we evaluated additional biomarkers tested by IHC, ISH and sequencing to further provide insight into therapeutic options for these epithelial ovarian tumors with or without BRCA mutations.

Results:

Table 1: Histological subtypes of epithelial ovarian tumors included:

Groups	N	Av. Age
All epithelial ovarian tumors included in this study	1691	61.6
Serous ovarian cancer	1058	62.7
Adenocarcinoma, not otherwise specified (NOS)	168	62
Clear cell ovarian cancer	77	56.7
Carcinosarcoma (MMMT)	67	65.4
Endometrioid	46	54.7
Mucinous	45	53
Carcinoma, NOS	230	60.5

Figure 1. Prevalence of Histological Subtypes

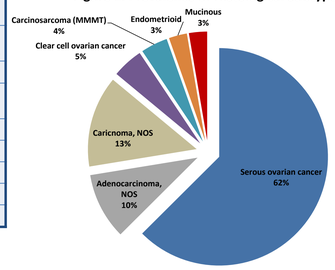


Figure 2: BRCA1 mutation rates seen in all epithelial ovarian tumors and in various histological subtypes. The highest mutation rate of BRCA1 is seen in serous histology. BRCA1 mutation is absent in mucinous ovarian tumors. VUS: variant of unknown significance.

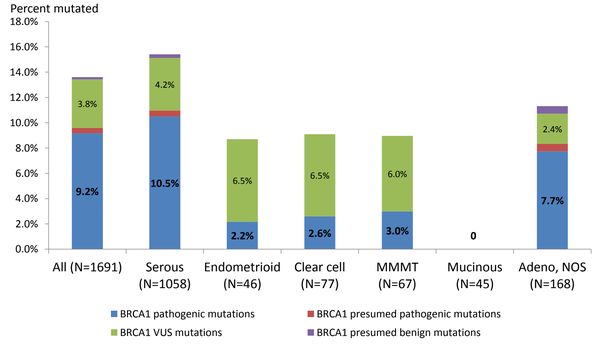


Figure 3: BRCA2 mutation rates seen in all epithelial ovarian tumors and in various histological subtypes. The highest mutation rate of BRCA2 is seen in serous histology and the lowest in mucinous.

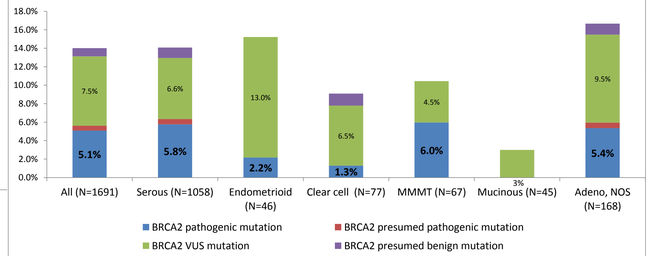
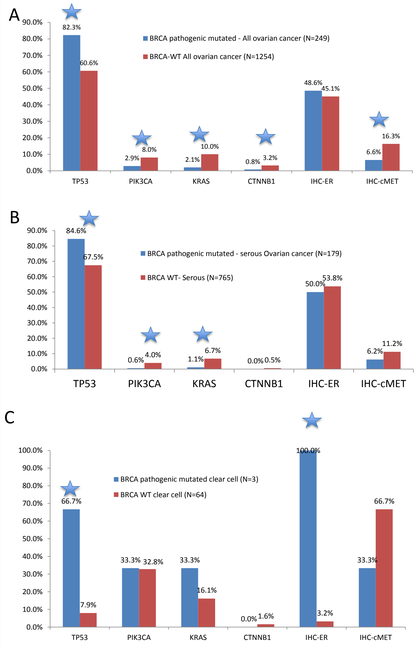
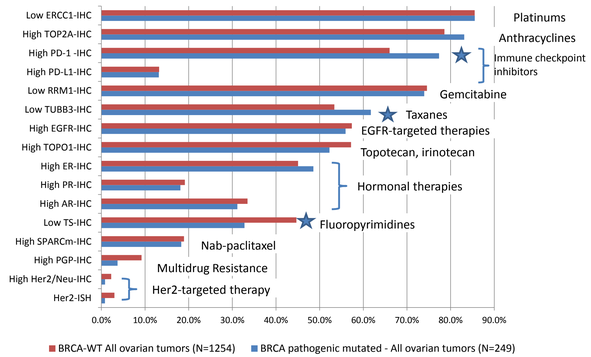


Figure 4: Selected biomarkers differentially aberrant in BRCA-mutated and BRCA-wild type tumors. Stars indicate differences that are statistically significant between the two cohorts. A: all epithelial ovarian tumors; B. serous ovarian tumors; C: clear cell ovarian tumors.



- When all histological subtypes are considered, TP53 mutation is significantly higher in BRCA-mutated tumors; whereas PIK3CA, KRAS and CTNNB1 mutations and cMET overexpression are higher in BRCA wild type tumors.
- Most of the aforementioned differences observed in the complete cohort persist in serous histology
- Clear cell histology has low patient numbers (77 in total) however ER is significantly associated with BRCA mutation.

Figure 5: Additional biomarkers tested by IHC and ISH in BRCA-WT and BRCA-MT epithelial ovarian tumors and associated therapies. Stars indicate differences that are statistically significant between the two cohorts.



Conclusions

- In epithelial ovarian cancer, BRCA mutations are seen in 14.3% of tumors. While serous histology shows the highest mutation rate, endometrioid, clear cell and carcinosarcoma all harbor various rates of BRCA mutations. Mucinous histology, however, rarely shows BRCA mutations.
- While BRCA-mutated patients carry a survival advantage and may benefit more from DNA-damaging agents including platinum agents and PARP inhibitors, BRCA-wild type tumors are more likely to carry PIK3CA, KRAS, CTNNB1 mutations and cMET overexpression that may serve as therapeutic targets.
- Even though clear cell ovarian cancer has been conventionally considered a hormone-independent histological subtype, our data suggest that in the rare event when deleterious BRCA mutations are found in clear cell ovarian tumors, estrogen receptor expression is high, suggesting a combination of hormonal therapies with either platinum or PARP inhibitors as a logical approach for clinical trial design.
- Biomarker frequencies indicate that the predicted benefit rate of commonly used chemotherapies including platinums, anthracyclines, gemcitabine and topotecan are similar in BRCA-mutated and wild type cohorts; on the other hand, fluoropyrimidines are more likely to benefit the BRCA-wild type cohort while taxanes are moderately but significantly more likely to benefit the BRCA-mutated cohort.
- BRCA-mutated and, therefore, homologous recombination deficient tumors, are more likely to harbor PD-1 positive tumor-infiltrating lymphocytes and can be further explored with immune checkpoint inhibitors.

References

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2. McNeish, et. al. " Results of ARIEL2: A Phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis " .