

ESGO 19

INTERNATIONAL MEETING OF
THE EUROPEAN SOCIETY OF
GYNAECOLOGICAL ONCOLOGY (ESGO)
OCTOBER 24-27, 2015 | NICE, FRANCE

European Gynaecological Oncology Congress 2015

OVERVIEW OF OVARIAN CANCER IN RELATION TO BRCA MUTATIONS

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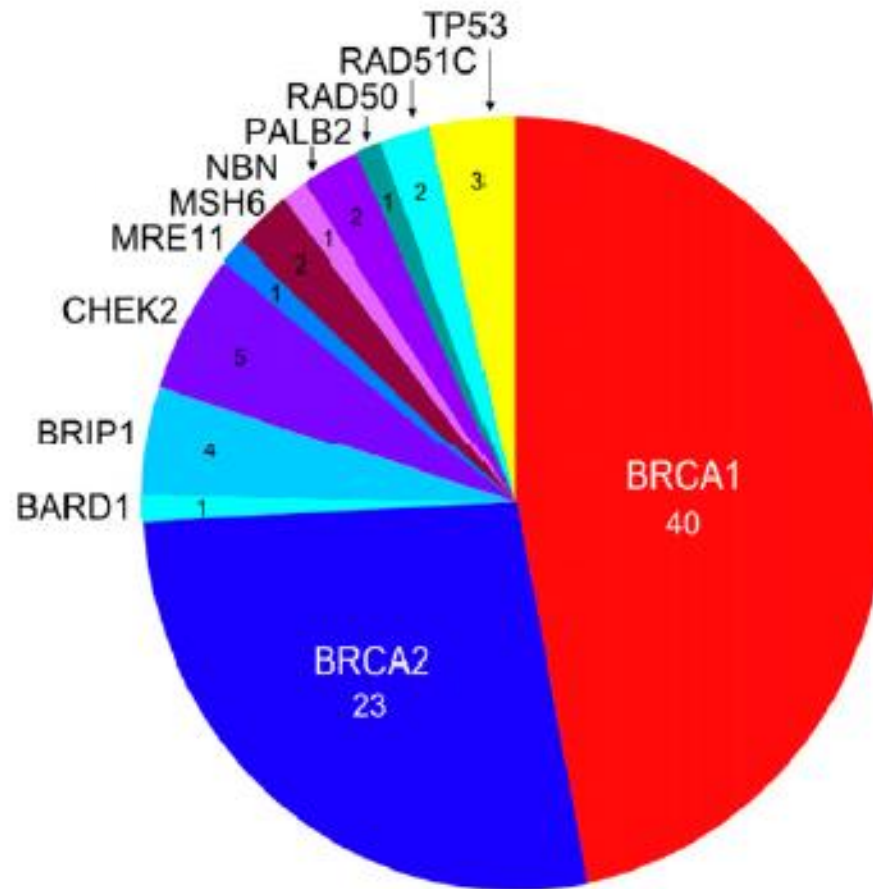
BRCA MUTATIONS

- BRCA – tumor suppressor genes
- BRCA1 and 2 proteins have integral functions in DNA homologous recombination repair (HRR).
- In normal cells, the HRR pathway is activated in response to DNA double-stranded breaks .
- In *BRCA 1/2*-deficient cells, HRR is impaired secondary to loss of *BRCA* function,
- Other more error-prone DNA repair pathways are activated.
- Causing, in part, carcinogenesis.

BRCA MUTATIONS

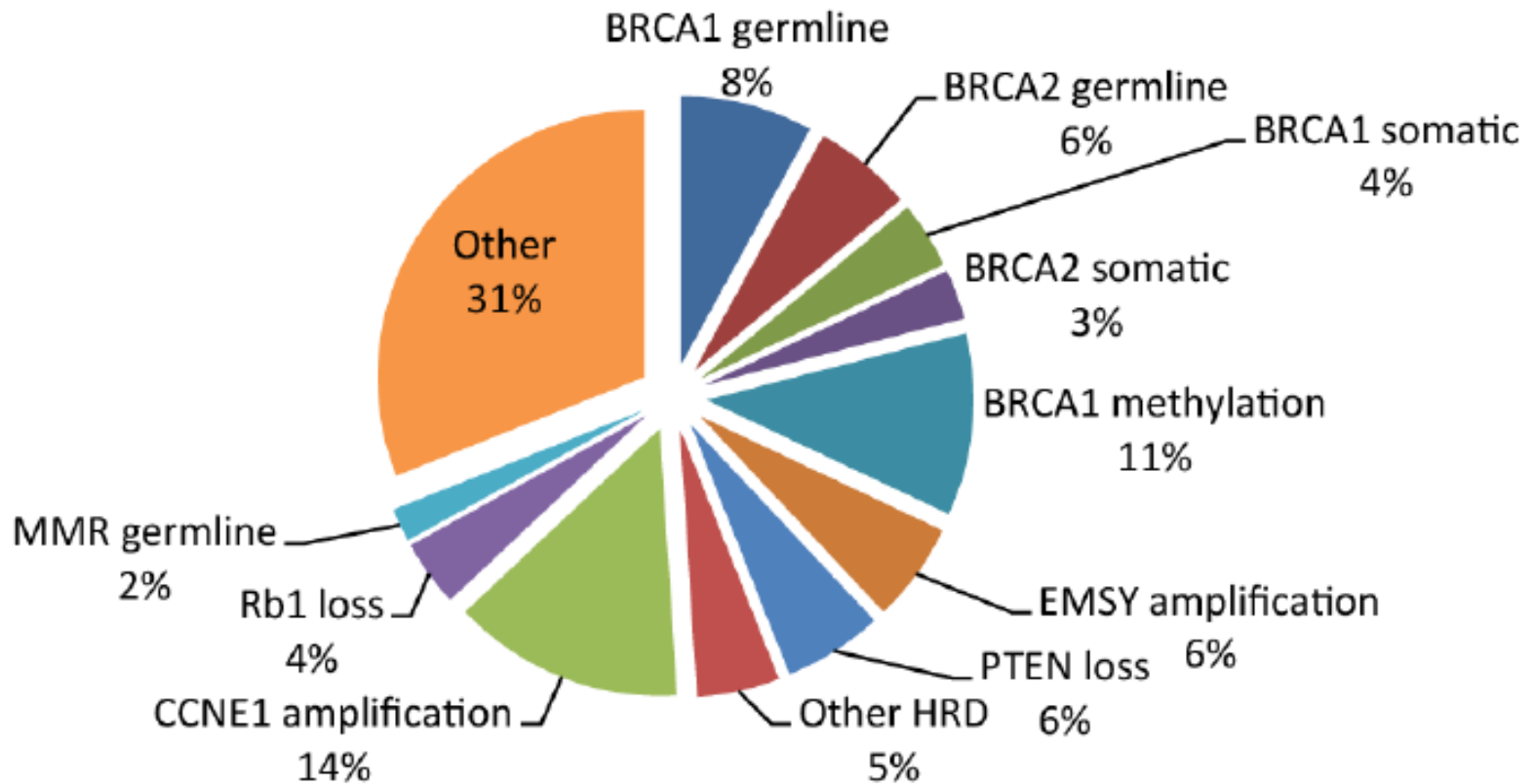
- We have gone a long way since the discovery of gBRCA mutations in 1994-1995
- It is now thought that up to 25% of all EOCs have a heritable component
- Even higher in founder populations: Poland, Finland, Iceland, French Canadian and Ashkenazi Jews

Inherited Mutations in EOC



EOC – Molecular Defects

Molecular Profiling of Serous Ovarian Cancer



Levine D, The Cancer Genome Atlas, 2011

gBRCA & BRCA-ness

Table 1. Some molecular defects that can lead to BRCAness

Defective mechanism	% in ovarian cancer
<i>BRCA1/2</i> germline mutation	10–15
<i>BRCA1/2</i> somatic mutation	5–10
<i>BRCA</i> promoter methylation	5–30
<i>EMSY</i> amplification	20
Fanconi anemia complex defects	21
<i>PTEN</i> focal deletion/mutation	7
<i>Rad51C</i> hypermethylation	3
<i>ATM/ATR</i> mutation	2

Rigakos G Razis E, The Oncologist 2012

- About 40-50% of EOC have some defect in HRR, with a large number of these being associated with BRCA-related defects
- Similar phenotypic characteristics to those with a hereditary BRCA mutation

gBRCA & BRCA-ness

- Type II tumors (70%):
 - **Serous,**
 - Carcinosarcoma
 - High grade endometroid
 - Clear cell
 - Tubal origin
 - ↑ P-53 mutation (almost 100% in HG serous)
- Response to treatment
- survival

gBRCA - Histology

Table 6

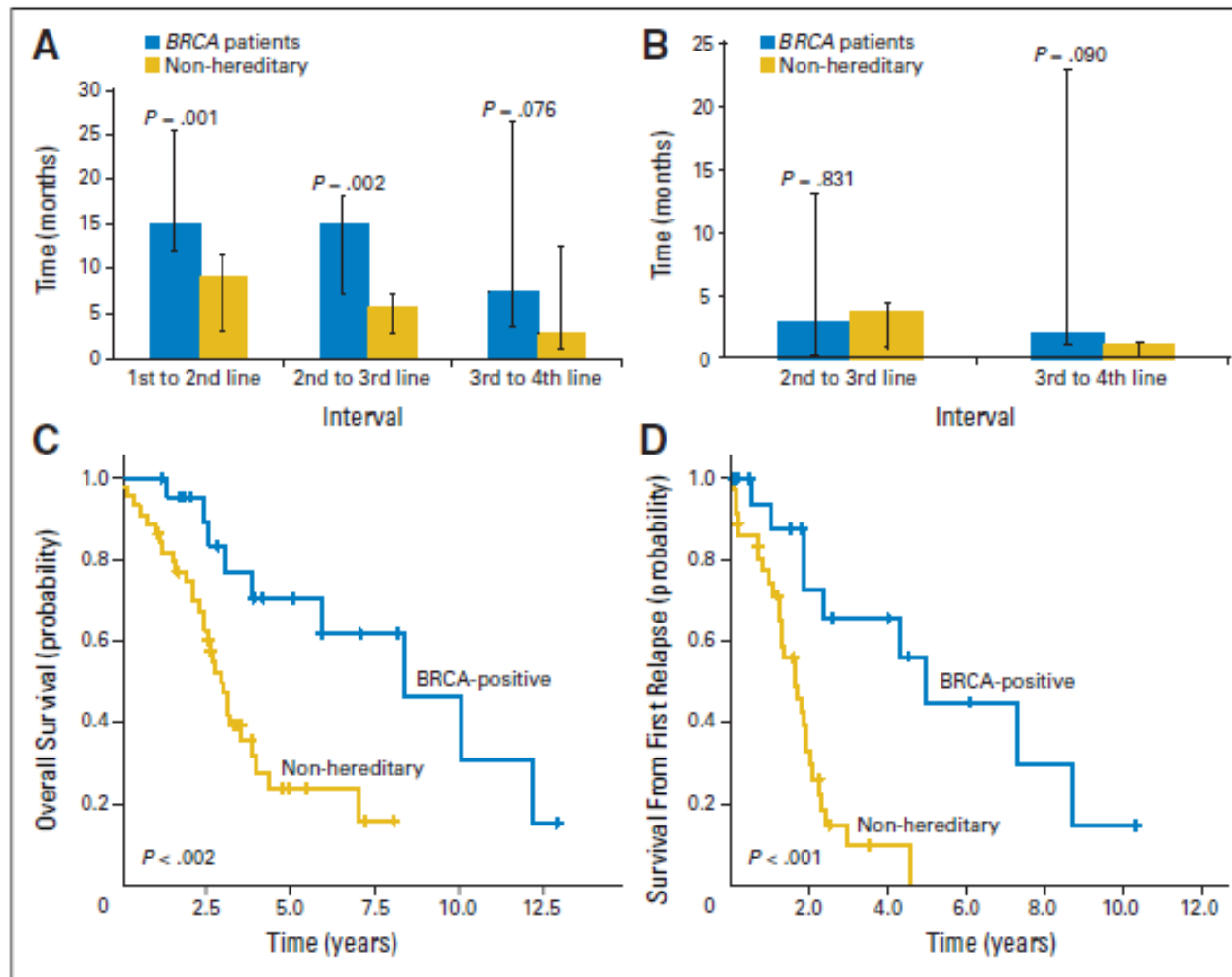
Frequency of mutations in cases of ovarian cancer by tumor histology.

Category	No. (%) positive for mutations in				Total no. of cases
	BRCA1	BRCA2	BRCA1 and BRCA2	Total	
Tumor histology					
Serous	81	52	2	135 (18.0%)	751
Endometrioid	18	8	0	26 (9.1%)	287
Mucinous	0	0	0	0 (0%)	112
Clear cell	1	1	0	2 (2.2%)	91
Carcinosarcoma	1	0	0	1 (7.1%)	14
Brenner	0	0	0	0 (0%)	4
Other	0	0	0	0 (0%)	4
Not specified	6	6	0	12 (15.2%)	79

gBRCA & BRCA-ness

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 - tumors with defective HRR mechanisms are more susceptible to the direct DNA damaging effects of chemotherapy.
- survival

Response to Chemotherapy



Response to Chemotherapy

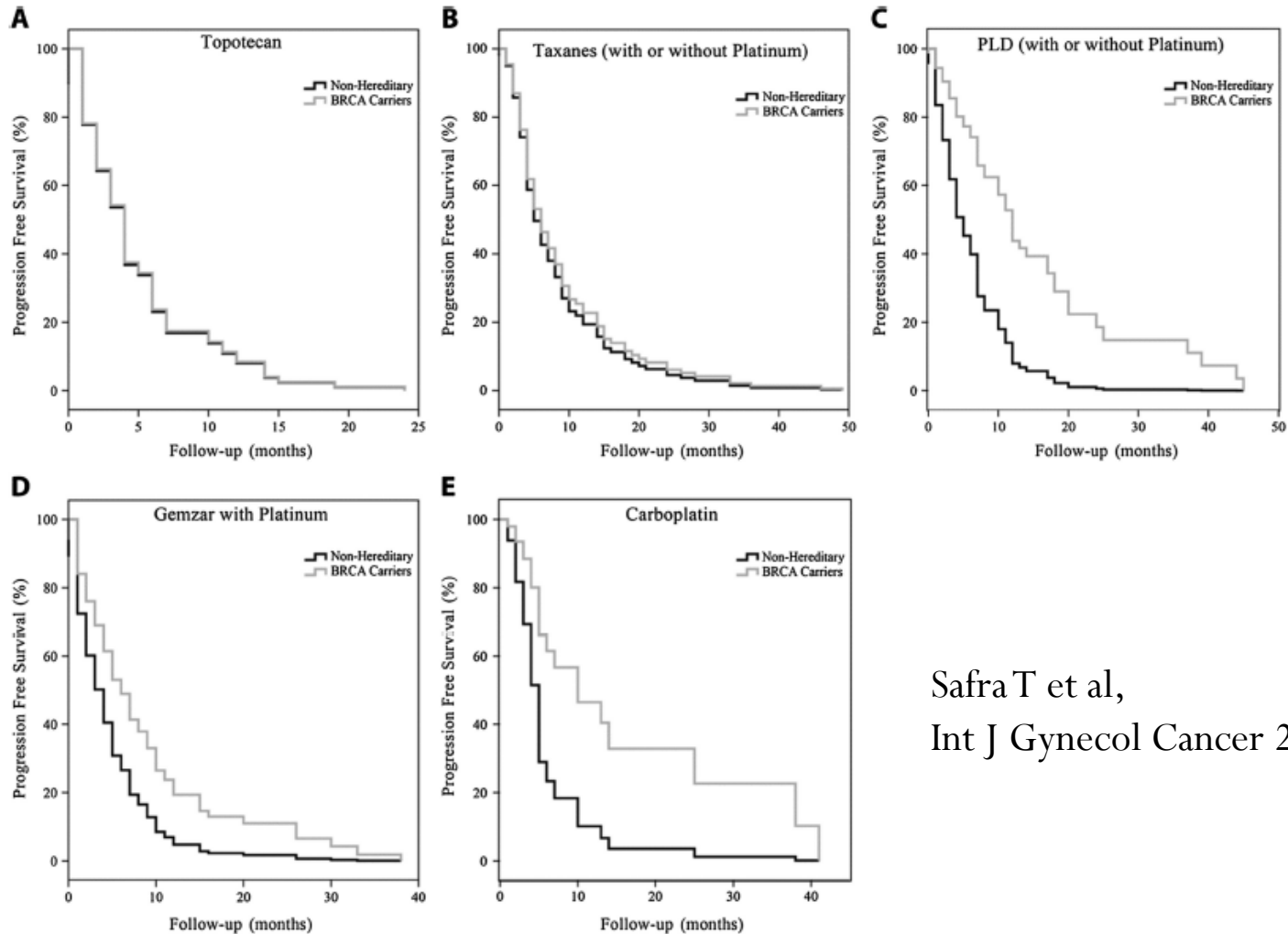
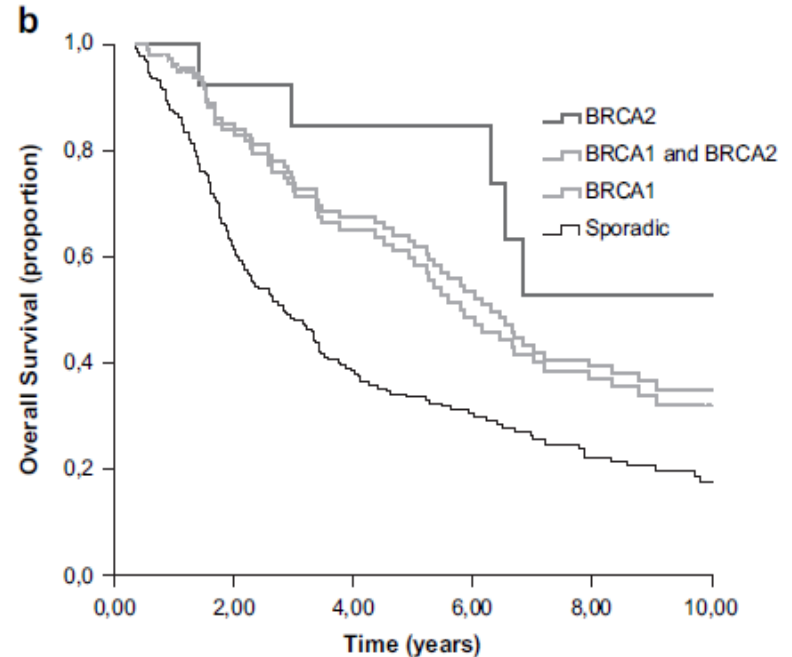
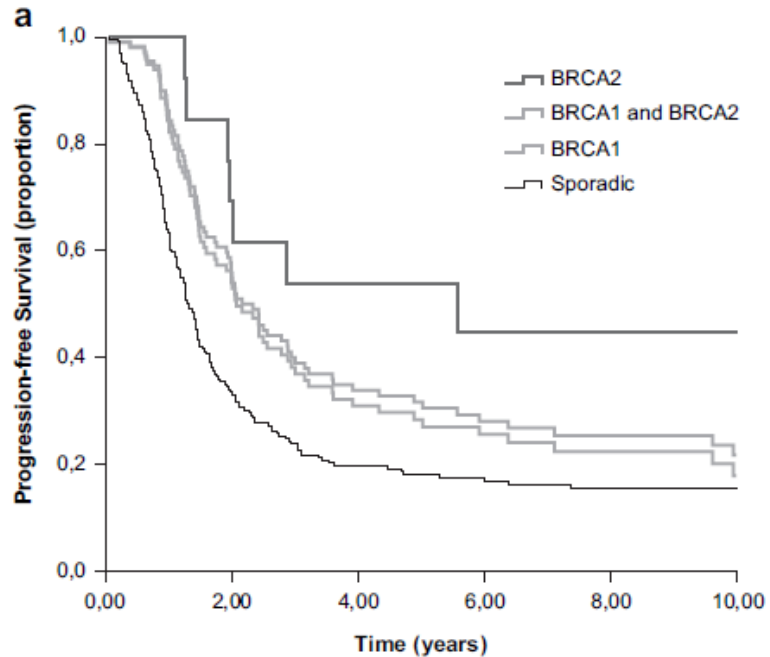


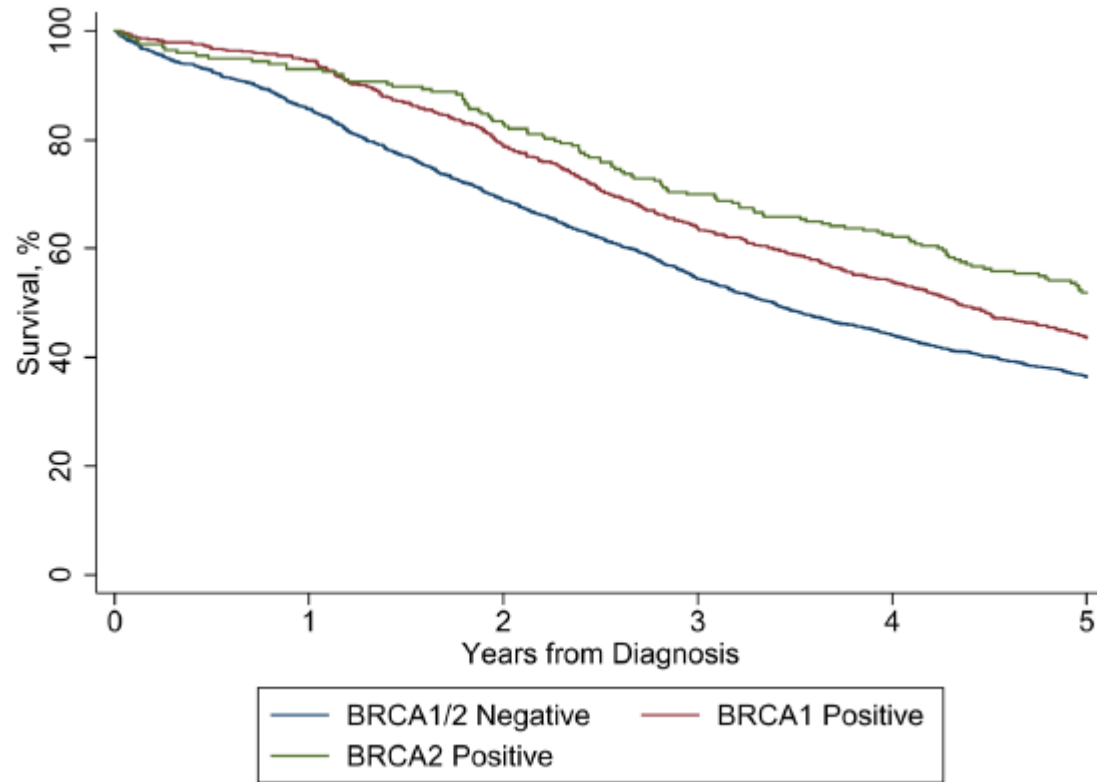
FIGURE 1. Comparison of PFS (months) of *BRCA* mutation carriers versus patients with NH disease.

Safra T et al,
Int J Gynecol Cancer 2014

Survival in Relation to BRCA Mutations



Survival in Relation to BRCA Mutations



Bolton et al JAMA 2012

26 studies, BRCA1 – 909, BRCA2-304, non carriers - 2666

Conclusions

- EOC is a heterogeneous malignancy with multiple defects in the HRR pathway
- These ovarian malignancies have similar biologic behavior
- Understanding the genetics will lead to better tailored treatment and improved survival