**Background**

- BRCA1 and BRCA2 mutations are found in 10-15% of unselected OC cases and up to 40% of heritable OC cases.
- Other genes including BRIP1, RAD51C, and RAD51D, have been associated with OC risk but magnitude of risk is less well defined.
- OC is an established feature of Lynch syndrome, but the relative contributions of the MMR genes in OC is less clear.
- Previous studies have been limited by:
  - Sample sizes large enough to estimate precise risks
  - Limited number of genes examined

**Methods**

**Multigene panel testing**

- Ambry cases were normalized to ExAC controls by removing.
- Variants were classified as pathogenic or very likely pathogenic.

**Study population**

- 10,233 ovarian cancer cases were referred to Ambry Genetics (Aliso Viejo, CA) for multigene panel testing between March 2012 and June 2016.

**Statistical analyses**

- Variants were classified as pathogenic or very likely pathogenic (PVLP) in cases and ExAC controls using a 5-tier system.
- Ambry cases were normalized to ExAC controls by removing LGRPs and variants in the PM22s pseudegene region from the analysis.
- Standardized risk scores (SRR) were calculated using observed frequency of PVLP variants in Ambry OC cases and summed frequency of all PVLP variants in ExAC.
- Odds ratios for the case-case analysis were calculated using observed frequency of PVLP variants in Ambry OC cases.

**Results**

- High-risk associations (SRR>4.0) for known OC genes: BRCA1, BRCA2, BRIP1, MSH6, RAD51C, and RAD51D.
- Moderate-risk associations (SRR=2.0-4.0) for suspected OC genes: ATM and PALB2.
- Attenuation of risks in sensitivity analyses:
  - PALB2 following removal of cases with breast cancer history.
  - MSH2 and MSH6 following removal of cases with colorectal cancer history.
- Associations with age at diagnosis:
  - ≤50: ATM, BRCA1, MSH2, and MSH6.
  - >60: BRIP1 and RAD51D.
- No significant associations with: BARD1, CDH1 (AC=10), CDKN2A (AC=1), CHEK2, MLH1, MRE11A, MUTHY, NBN, PALB2, PM2, PTEN, RAD51D, RAD51C, RAD53.

**Conclusions**

- We confirmed associations with OC risk for several known and suspected OC genes.
- These findings shed light on the current NCCN guidelines for Lynch syndrome mutation carriers as no association with OC was identified for MLH1 and MSH2.
- We provide more precise estimates than previously reported for genes including RAD51C and RAD51D.
- We did not find a significant association BARD1 which is a previously suspected OC gene.

**References**