Abstract Number: 5510 Presented at ASCO 2016

Ovarian Cancer Risk Associated with Mutations Detected by Multiple-Gene Germline Sequencing in 95,561 Women

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BACKGROUND

- Multi-gene panel testing approximately doubles mutation detection rate
  - *BRCA1/2*, Lynch Syndrome genes, *ATM*, *CHEK2*, *PALB2*, *STK11*, *TP53*, *NBN*, *CDH1*, etc.
- Uncertainty about magnitude of ovarian cancer risk with unfamiliar genes
- Recommendations (e.g., salpingo-oophorectomy) depend on risk level
- Most penetrance studies to date are relatively under-powered

METHODS

Patients and Genetic Testing

- Patient population: 95,561 women, tested clinically
  - September 2013-2015 (period of availability of multiple-gene panel)
  - Exclusions: missing data fields on requisition form, prior testing
- Data collection: Clinical testing requisition forms
  - Completed by ordering clinician
  - Queried personal and family cancer history, racial/ethnic ancestry
- Genetic testing: 25-gene hereditary cancer panel (Myriad)
  - Full sequencing and comprehensive rearrangement analysis
  - Standard variant classification approach (Am. College of Med. Genetics)

Statistical Analysis

- Primary method: Multivariable logistic regression
  - Dependent variable: Ovarian cancer
  - Independent: Age, race/ethnicity, personal and family cancer history
  - Wald statistic used to calculate odds ratios with 95% confidence interval
  - Interpretation: Risk due to mutation, after accounting for other variables
- Secondary method: Case-control study matched on age, race, family hx
  - Exact McNemar's test used to estimate odds ratios, 95% CI
  - Intended as a sensitivity analysis on results of logistic regression

RESULTS

- Table 1 shows that 5% of women in this cohort had a personal diagnosis of ovarian cancer.
- The median age of the overall cohort was 48 years, compared to 62 years for women with ovarian cancer.

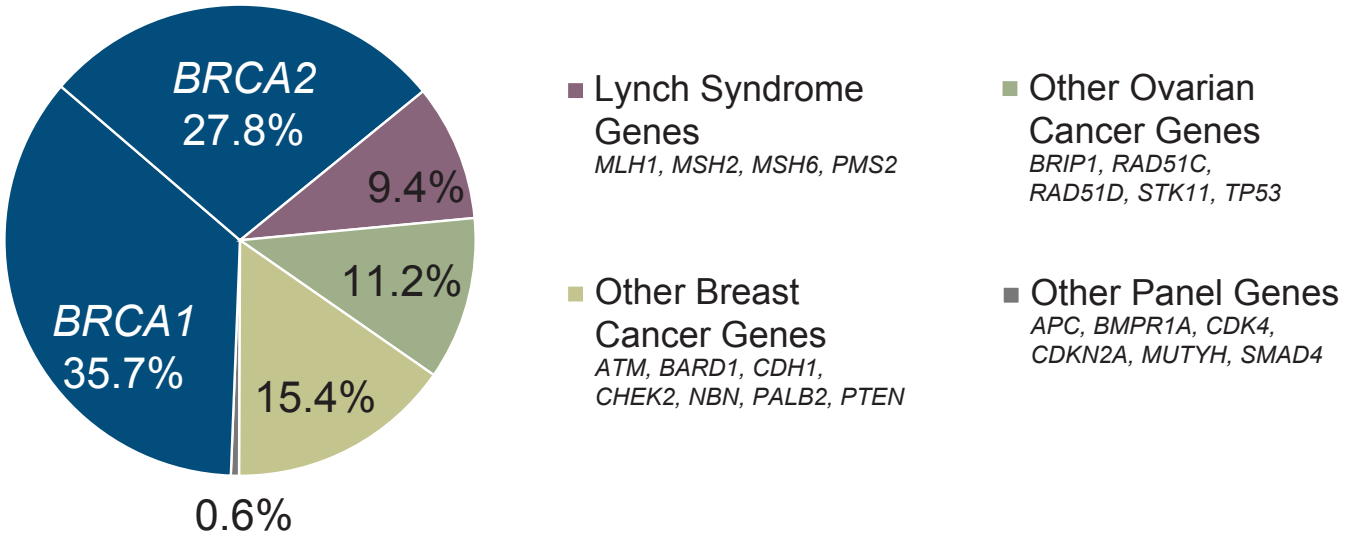
Table 1. Patient Characteristics

		All Patients (%)	OC Cases (%)
	Total Patients*	95,561 (100)	5,020 (5)
Age at Genetic Testing	Range	11-98	20-97
	Median	48	62
	% Age ≤ 50 years	57	20
Ancestry	Western/Northern European	54,372 (57)	3,359 (67)
	Central/Eastern European	13,134 (14)	543 (11)
	Latin American/Caribbean	8,915 (9)	405 (8)
	African	8,829 (9)	254 (5)
	Native American	3,925 (4)	174 (3)
	Asian	3,195 (3)	169 (3)
	Ashkenazi	2,211 (2)	80 (2)
	Near or Middle Eastern	980 (1)	35 (1)
Family Cancer History	One or More FDR with OC	11,396 (12)	392 (8)

FDR, First degree relative; OC, Invasive epithelial ovarian

- 7% (6,626) of all patients had ≥1 mutation.
- 14% (701) of patients with ovarian cancer had ≥1 mutation (Figure 1).

Figure 1. Distribution of Pathogenic Mutations



RESULTS

- Multivariable regression showed significant associations with ovarian cancer for 11 genes (Table 2, Figure 2).
  - 2-fold to 40-fold elevations in ovarian cancer risk.
- There is a high degree of correlation between the multivariate regression and matched case-control results (Figure 3).

Figure 2: Odds Ratios, Logistic Regression

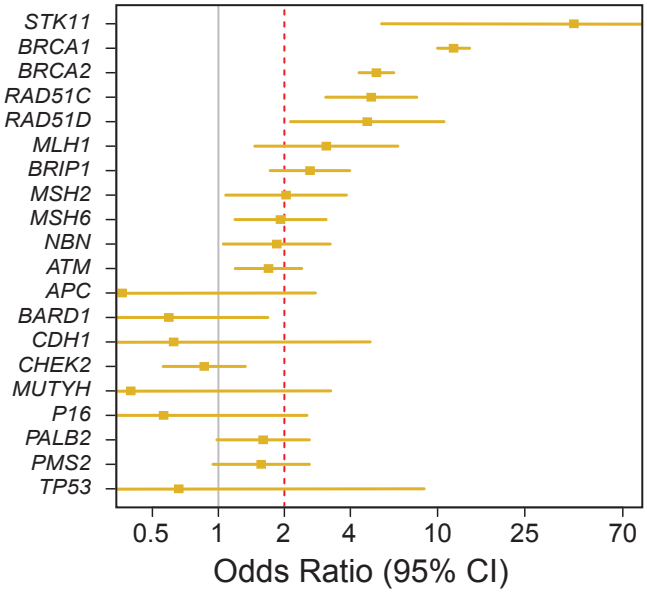
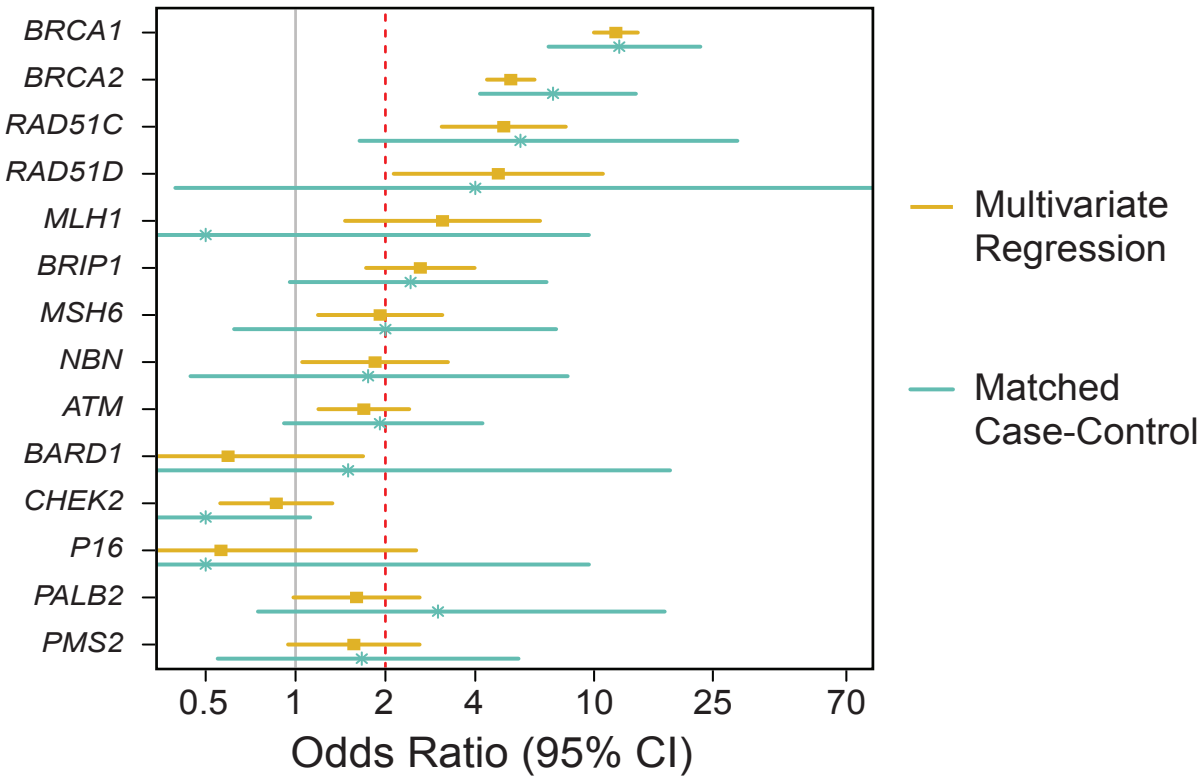


Table 2: Multivariable Regression Results

Gene	OR	95% CI	P-Value
STK11	41.9	5.55, 315	2.9×10^{-04}
BRCA1	11.8	9.99, 14.0	6.2×10^{-181}
BRCA2	5.26	4.38, 6.31	1.0×10^{-70}
RAD51C	4.98	3.09, 8.04	4.6×10^{-11}
RAD51D	4.78	2.13, 10.7	1.4×10^{-04}
MLH1	3.11	1.47, 6.59	0.0031
BRIP1	2.62	1.72, 3.98	6.4×10^{-06}
MSH2	2.04	1.08, 3.84	0.028
MSH6	1.92	1.19, 3.10	0.0076
NBN	1.85	1.05, 3.24	0.032
ATM	1.69	1.19, 2.40	0.0032

OR, Odds ratio; CI, Confidence interval

Figure 3: Odds Ratios, Comparing Approaches



CONCLUSIONS

- 11 genes associated with significant OC risk increase (2- to 40-fold)
  - STK11, BRCA1, BRCA2, RAD51C, RAD51D, MLH1, BRIP1, MSH2, MSH6, NBN, ATM
  - First report of OC risk with ATM (~0.5%-1% of breast cancer patients)
- 14% of all OC patients had at least one pathogenic mutation
- Nearly 1/3 were in non-BRCA1/2, non-Lynch Syndrome genes
  - 15.4% in “breast cancer genes”, 11.2% in “ovarian cancer genes”
  - Panel testing may reveal a broader spectrum of associated cancers

LIMITATIONS AND QUESTIONS RAISED

- Data collection
  - Clinical testing sample; not accrued prospectively for research purposes
  - Patient characteristics, family history were derived from clinician report
- Analytic approach
  - Could not use a kin-cohort approach (not a family study)
  - Two other methods (logistic regression, case-control) largely consistent
- Other patient populations
  - May not generalize to unselected cancer patients
  - However, does represent “real-world” testing scenarios

FUTURE DIRECTIONS

- Penetrance, prevalence in other populations
  - Unselected cancer patients (breast, ovarian, other)
  - Enriched for racial/ethnic minorities
  - Evolving gene panels
  - Correlation with somatic mutations, tumor pathogenesis
- Complementary and confirmatory study designs
  - Validate report of patient and family cancer history
  - Testing of relatives, kin-cohort analysis
  - More clinical detail (tumor features, treatment, outcomes)