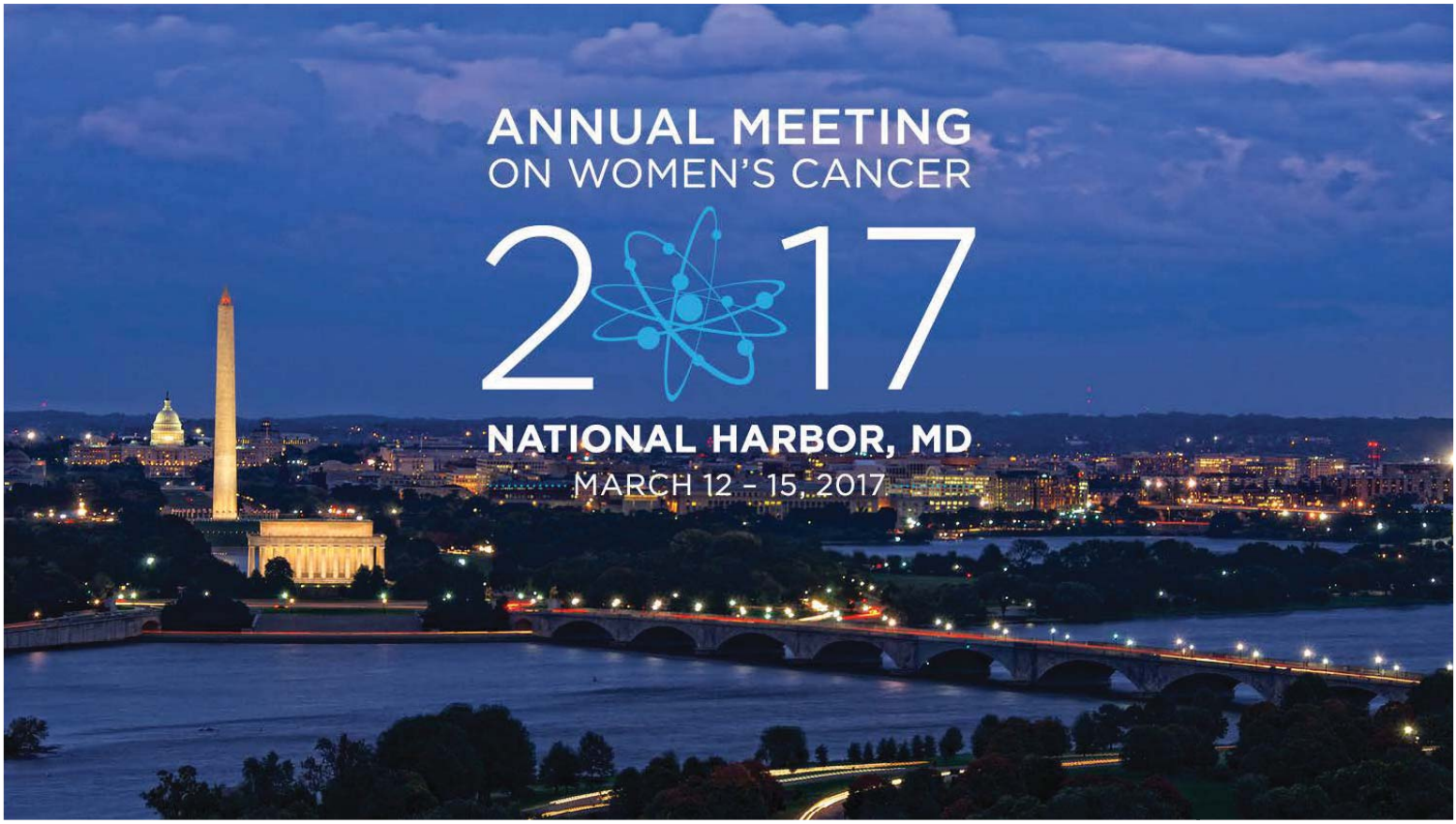


A description of women with the pathogenic variants in the ovarian cancer risk genes *BRIP1*, *RAD51C*, *RAD51D* identified through clinical testing with a hereditary cancer panel

Lydia Usha[1], Susana San Roman[2], Heidi Gorringe[2], Ryan Bernhisel[2], Krystal Brown[2], Jennifer Saam[2], Susan Manley[2]

[1]Rush University Medical Center, Chicago, IL [2]Myriad Genetic Laboratories, Inc., Salt Lake City, UT

ANNUAL MEETING ON WOMEN'S CANCER 2017 NATIONAL HARBOR, MD MARCH 12 - 15, 2017

Bringing Together the Best in Women's Cancer Care

Presented at SGO March 15, 2017

Background

- The NCCN recommends that risk-reducing salpingo-oophorectomy be considered for women with mutations in *BRCA1*, *BRCA2*, and the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*).
- Recently, *BRIP1*, *RAD51C* and *RAD51D* have been shown to confer increased risk for ovarian cancer and have been added to NCCN guidelines.
- However, the mean age of ovarian diagnosis for patients with mutations in these genes is less known.
- The median age of ovarian cancer diagnosis is important for optimal cancer prevention.

Objectives

Gene	NCCN Guidelines Management Recommendations
BRCA1/BRCA2	Recommend RRSO "typically between 35 and 40 y and upon completion of child bearing" "it is reasonable to delay RRSO until age 40-45 y in patients with *BRCA2* mutations"
BRIP1	Consider RRSO at 45-50 years
RAD51C	Consider RRSO at 45-50 years
RAD51D	Consider RRSO at 45-50 years

- Here, we investigate the clinical presentation of women who carry a mutation in *BRIP1*, *RAD51C*, or *RAD51D*

Daly M, et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2017.

Methods

- We assessed women who were found to carry a mutation in *BRIP1*, *RAD51C*, or *RAD51D* via testing with a 25-gene hereditary cancer panel between September 2013 and December 2016, which includes full sequence and large rearrangement analysis.
- Clinical information was obtained from the provider-completed test request form.
- Personal and family history of ovarian cancer and age-at-diagnosis were evaluated according to gene.
- Women with mutations in *BRCA1*, *BRCA2*, or the MMR genes were assessed for comparison.

Positive Mutation Rates for Women Tested

	Total Women (%)	Women with OC (%)
Women tested	345,667	18,719
BRIP1	975 (0.3%)	151 (0.8%)
RAD51C	475 (0.1%)	104 (0.6%)
RAD51D	206 (0.1%)	39 (0.2%)
BRCA1	4158 (1.2%)	657 (3.5%)
BRCA2	4653 (1.3%)	504 (2.7%)
Total for above genes	**10,467 (3.0%)**	**1455 (7.8%)**

- 1656 tested women had a mutation in *BRIP1*, *RAD51C*, or *RAD51D*

ANNUAL MEETING ON WOMEN'S CANCER 2017 NATIONAL HARBOR, MD MARCH 12 - 15, 2017

Bringing Together the Best in Women's Cancer Care

Positive Mutation Rates for Women with OC

	Fallopian Tube	Peritoneal	Ovary	All OC
Women tested	499	370	17,850	18,719
BRIP1	8 (1.6%)	2 (0.5%)	141 (0.8%)	151 (0.8%)
RAD51C	3 (0.6%)	0	101 (0.6%)	104 (0.6%)
RAD51D	1 (0.2%)	0	38 (0.2%)	39 (0.2%)
BRCA1	23 (4.6%)	21 (5.7%)	613 (3.4%)	657 (3.5%)
BRCA2	18 (3.6%)	12 (3.2%)	474 (2.7%)	504 (2.7%)
Total for above genes	**53 (10.6%)**	**35 (9.5%)**	**1367 (7.7%)**	**1455 (7.8%)**

Only first ovarian cancer diagnosis type is included for women with multiple diagnoses

- There was no substantial differences in the gene-specific positive rate for the different types of ovarian cancer

Mutation Prevalence by Ethnicity

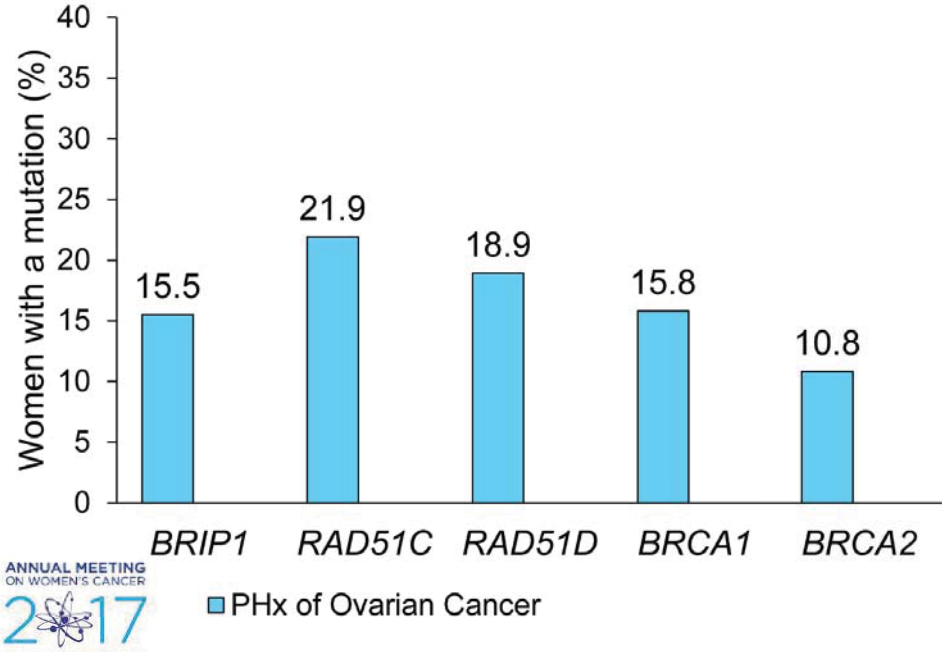
	BRIP1	*RAD51C*	*RAD51D*	Total
African	48 (0.2%)	40 (0.2%)	24 (0.1%)	112 (0.5%)
Asian	16 (0.2%)	17 (0.2%)	17 (0.2%)	50 (0.6%)
European*	552 (0.3%)	241 (0.1%)	104 (0.1%)	897 (0.5%)
Latin Am/Carib.	60 (0.2%)	41 (0.2%)	11 (<0.1%)	112 (0.4%)
Other**	27 (0.3%)	11 (0.1%)	9 (0.1%)	47 (0.5%)
Multiple Indicated	57 (0.3%)	31 (0.1%)	12 (0.1%)	100 (0.5%)
None Specified	215 (0.3%)	94 (0.1%)	29 (<0.1%)	338 (0.4%)
Total	**975**	**475**	**206**	**1656**

*Includes Western/Northern, Central/Eastern Europe, Ashkenazi Jewish, and any combination of only those 3
**Includes Near/Mideast, Native American, and Other

ANNUAL MEETING ON WOMEN'S CANCER 2017 NATIONAL HARBOR, MD MARCH 12 - 15, 2017

Bringing Together the Best in Women's Cancer Care

Incidence of OC among Mutation Carriers

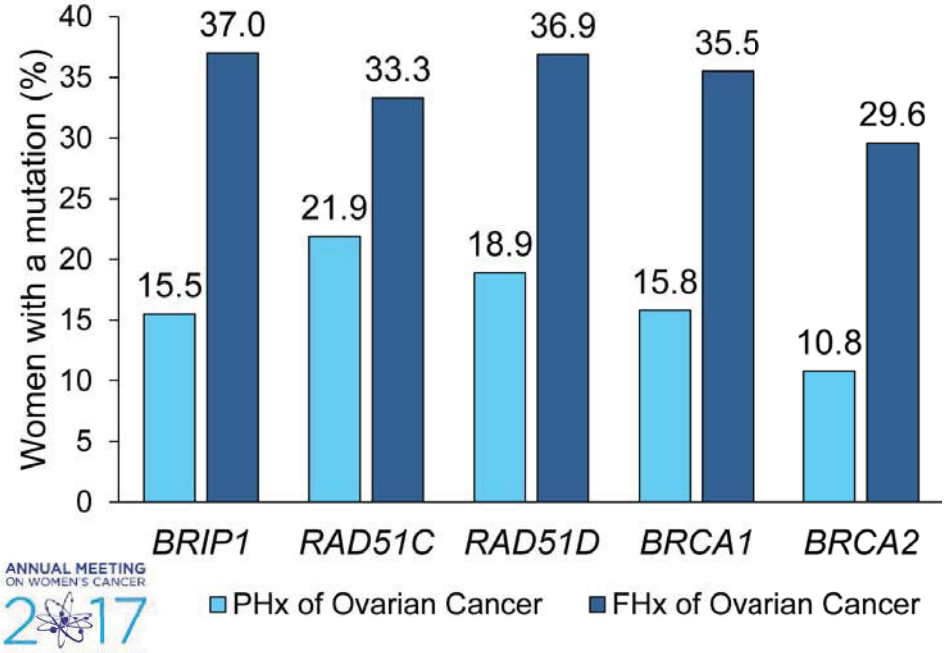


- Women with a mutation in *RAD51C* had the highest incidence of ovarian cancer of the genes evaluated.
- The incidence of ovarian cancer among women with a mutation in *BRIP1* and *RAD51D* was similar to *BRCA1* and higher than *BRCA2*

ANNUAL MEETING ON WOMEN'S CANCER 2017 NATIONAL HARBOR, MD MARCH 12 - 15, 2017

Bringing Together the Best in Women's Cancer Care

Women with Family History of OC

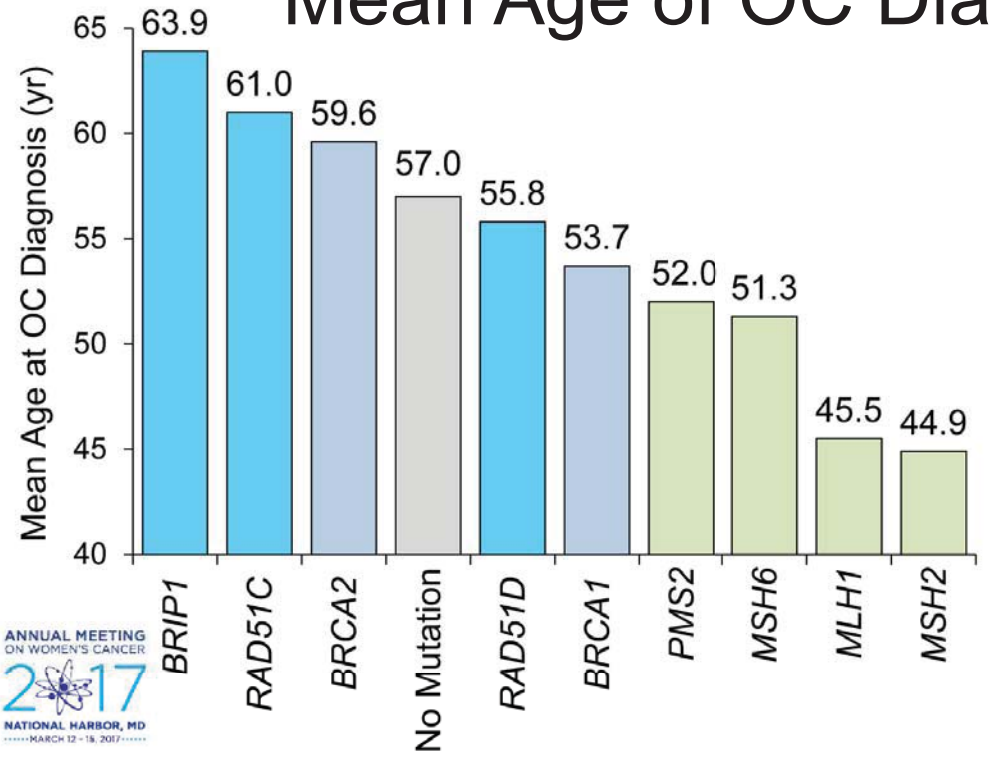


- There was a similar incidence of ovarian cancer in ≥1 first or second degree relative among women with a mutation in *BRIP1*, *RAD51C*, *RAD51D*, or *BRCA1.*

ANNUAL MEETING ON WOMEN'S CANCER 2017 NATIONAL HARBOR, MD MARCH 12 - 15, 2017

Bringing Together the Best in Women's Cancer Care

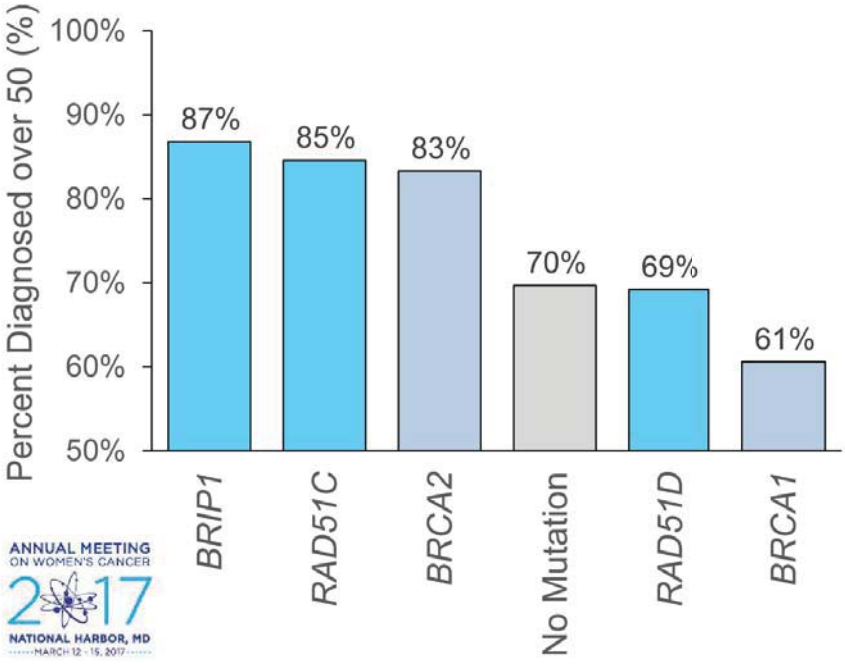
Mean Age of OC Diagnosis



- Diagnosis age for women with a mutation in *BRIP1*, *RAD51C*, and *RAD51D* was
  - Similar to women with a variant in *BRCA2*
  - Slightly older than women with a variant in *BRCA1* or one of the MMR genes.

Bringing Together the Best in Women's Cancer Care

Carriers Diagnosed with OC after Age 50



- Over 80% of women with ovarian cancer who had a mutation in *BRIP1, RAD51C,* and *BRCA2* were diagnosed after 50.
- Women with Mutations in *RAD51D* are more similar to *BRCA1* mutation carriers in diagnosis age

Bringing Together the Best in Women's Cancer Care

Presented at SGO March 15, 2017

Conclusions

- Collectively, this may aid clinical decisions regarding the medical management for women with mutations in these three genes.
- Our data supports delaying RRSO in *BRIP1*, *RAD51C*, *RAD51D* mutation carriers until the age of 45 – 50. This avoids the psychosocial and medical complications of premature menopause.
- Our data indicate that women with *BRIP1* mutations can safely delay RRSO until the age of 50.
- Our data informs carriers of mutations in these genes on their ovarian cancer risk. It may also assist in reproductive decisions such as the age of childbearing.