Association of *BRCA1* Mutations with Impaired Ovarian Reserve: Connection Between Infertility and Breast/Ovarian Cancer Risk

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Purpose: Mutations in the *BRCA1/2* genes are associated with breast and ovarian cancer susceptibility. Recent studies have suggested that the *BRCA* mutation might be associated with occult primary ovarian insufficiency. To evaluate fertility, several studies have validated anti-Mullerian hormone (AMH) as a direct biomarker for ovarian aging and it is considered a quantitative marker of ovarian reserve. We hypothesize that *BRCA1* gene mutations will be negatively associated with AMH levels.

Methods: We evaluated 124 women aged 18–45 years participating in the Northwestern Ovarian Cancer Early Detection and Prevention Program. Patients with a history of cancer, ovarian surgery, or exposure to chemotherapy were excluded. Linear and logistic regression modeling were performed to evaluate the association between AMH levels, age, and *BRCA1* mutation. In logistic models, the outcome ‘low AMH’ was defined as AMH <0.05 ng/mL. Logistic regression models were used to adjust for other factors, including body mass index (BMI), duration of birth control (BC), smoking, gravidity, and parity.

Results: Women with the *BRCA1* mutation had a significant decline in AMH with age ($p=0.0011$). *BRCA1*-positive women >35 years had 10 times the odds of a low AMH (<0.5 ng/mL) compared with women ≤35 years. With adjustment for BMI, duration of BC, smoking, gravidity, parity, and age >35, *BRCA1* was still strongly associated with a low AMH ($p=0.037$).

Conclusion: Women >35 with the *BRCA1* mutation have a lower AMH, and hence ovarian reserve, than women without a *BRCA* mutation. Therefore, young adults with the *BRCA1* mutation should be counseled regarding this potential decrease in ovarian reserve.

Keywords: BRCA, anti-Mullerian hormone, ovarian reserve, BRCA mutation

Introduction

MUTATIONS IN THE *BRCA1* and *BRCA2* genes are associated with breast and ovarian cancer susceptibility.^{1,2} This has clinical significance as one in every 1000 women are *BRCA* positive, with the incidence being as high as 2.5% in certain ethnic groups, including those of Ashkenazi Jewish descent.^{1–4} Lifetime risk estimates indicate that 15%–40% of women who have a *BRCA1* or *BRCA2* mutation

will be diagnosed with ovarian cancer compared with 1.4% of women in the general population.

BRCA genes are activated during gametogenesis and early embryogenesis and play an essential role in double-strand DNA break repair. They participate in the repair and maintenance of chromosome telomere integrity, which is important during reproduction.^{5–8} Telomeres, which shorten after each cycle of DNA replication, have been implicated as one of the determinants of a person’s reproductive lifespan. In

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addition to telomere length, factors affecting cell cycle division and DNA repair may also affect a reproductive lifespan.⁸ Given the range of functions of the BRCA proteins, it is reasonable to believe that defects in these genes may affect reproduction.

Research has suggested an association with the BRCA mutation and occult primary ovarian insufficiency.^{9,10} In one study, low ovarian response was significantly higher in *BRCA1* mutation-positive patients compared with BRCA mutation-negative patients, suggesting an association between *BRCA1* mutations and diminished oocyte reserve. Ovarian reserve markers were not included in this study. A similar trend was noted in another study examining ovarian response in patients undergoing fertility preservation.⁹

However, results are inconsistent as another matched case-control study examining BRCA carriers and noncarrier controls from the same families suggested that there was little to no effect of the BRCA gene mutation on parity and fertility.¹⁰ However, given the young age of the participant's first and last birth (25.6 and 29.9 years, respectively), any potential differences in fertility existing toward the end of the reproductive life could not be examined in this study. In addition, this study did not examine markers of ovarian reserve.

Several studies have validated anti-Müllerian hormone (AMH) as a direct biomarker for ovarian aging^{11,12} and it is currently considered a quantitative marker of ovarian reserve. Animal studies have shown AMH to play a role in the primary follicle depletion rate and its values appear to correspond well with antral follicle counts and ovarian response to hyperstimulation during *in vitro* fertilization.^{11–15} In addition, AMH has been the marker that best reflects the gradual decline in reproductive capacity with increasing age.¹¹ Due to its presumed menstrual cycle independence, it is also valued as a marker for ovarian reserve.^{11,14}

Given the functions of the BRCA gene as well as the results from published literature, we hypothesized that mutations in the *BRCA1* gene would be associated with lower AMH levels. In addition, we hypothesized that in addition to AMH, factors like age, smoking history, body mass index (BMI), low gravidity/parity, may be possible risk factors for low AMH.^{16–21} These results may provide additional information regarding reproductive health in *BRCA1* carriers, especially with regard to family building.

Methods

Selection of patients

The Institutional Review Board of Northwestern University approved the study. Eligible subjects were drawn from Northwestern University's Ovarian Cancer Early Detection and Prevention Program (NOCEDPP), a clinical and research program at Northwestern University. All participants had previously provided written informed consent to have blood drawn for research purposes at their initial visit and at every 6-month visit. Women were eligible for this program if they had a personal history of breast, ovarian, or colon cancer; had one or more first-degree relatives with ovarian, primary peritoneal, or fallopian tube cancer; had two or more family members with either breast, ovarian, primary peritoneal, fallopian tube, colon, uterine and/or pancreatic cancer; or had a personal or family history of a hereditary

cancer syndrome, including a *BRCA1* or *BRCA2* mutation. For this study, inclusion criteria included females, ages 18–45 years, and previous BRCA testing. Published research has suggested an association with *BRCA1* mutation carriers and not *BRCA2* mutation carriers, and for that reason exclusion criteria included *BRCA2* mutation carriers, those with mutations of undetermined significance, women with a personal history of cancer or exposure to chemotherapy, and women with a history of a unilateral or bilateral oophorectomy or other ovarian surgery.

Study design

AMH levels were checked on stored serum from this cohort who met our inclusion and exclusion criteria. Clinical and demographic data were also obtained, including age, race, BMI (kg/m²), gravidity, parity, duration and type of birth control (BC), current smoking status, and history of tamoxifen use. We also obtained pertinent surgical, gynecological, and medical history.

The primary outcome was AMH level. This was assayed using stored serum from a woman's first encounter with the NOCEDPP. For this study, we defined low AMH as AMH <0.5 ng/mL. AMH values ranging from 0.5 to 1.0 ng/mL are considered a low AMH and clinical experience at Northwestern University supports using <0.5 mg/mL as corresponding with a low AMH. The covariates that were selected as possible risk factors for infertility were obtained by performing a detailed chart review as described above.

AMH values were assayed from blood samples that were obtained at the first visit with the NOCEDPP. These frozen aliquots were thawed for analysis. The AMH ELISA Kits were used (Beckman Coulter, Inc., Brea, CA) following the manufacturer's directions. The lower limit of detection with this kit was 0.10 ng/mL.

Statistical analysis

Baseline characteristics of subjects with and without the *BRCA1* mutation were compared using Fisher's exact test for categorical variables or two-sample *t*-tests for continuous factors. Wilcoxon rank-sum test was used to see the relationship between *BRCA1* mutations and AMH levels. Regression analyses were performed to evaluate AMH levels, age, and *BRCA1* mutation associations. First, linear regression was used to evaluate associations between age and AMH level for *BRCA1*-positive and BRCA mutation-negative women. AMH values were log transformed due to the skewed nature of the observed AMH levels and to adhere to the assumptions of the linear regression models. AMH level was the outcome, and covariates included main effects of *BRCA1* mutation and age, and an interaction between the *BRCA1* mutation and age. Graphical diagnostics were used to address model assumptions.

Logistic regression was then used with low versus high AMH as the outcome variable (low AMH defined as AMH <0.5 ng/mL) with the same independent variables as described above. The odds ratios (ORs) from the resulting model represent the risk of low AMH versus high AMH for one unit difference in the covariate. In addition to age and *BRCA1* mutation, in logistic models we also included obesity (BMI ≥ 30), duration of BC, current smoking status, gravidity (at least one pregnancy vs. none), and parity (at least

TABLE 1. DEMOGRAPHIC INFORMATION

Patient characteristics n = 124	BRCA-negative n = 56	BRCA1-positive n = 68	p-Value
Age (years)			
≤ 35	23 (41%)	45 (66%)	0.007
>35	33 (59%)	23 (34%)	
AMH level, mean level (ng/mL)	3.49	3.58	0.36*
Race			
White	39 (72%)	50 (74%)	0.15
Other (Asian, African American, Hispanic, American Indian)	9 (17%)	4 (6%)	
Unknown**	8 (11%)	14 (21%)	
Smoking (current)	1 (1%)	4 (6%)	0.30
BMI (kg/m ²)	24.4	23.9	0.59
Obesity			
BMI >30	5 (10%)	5 (8%)	0.76
BMI ≤ 30	46 (90%)	61 (92%)	
Gravidity			
One or more pregnancy	38 (68%)	29 (43%)	0.007
No pregnancies	18 (32%)	38 (57%)	
Parity			
One or more full-term pregnancy	33 (59%)	27 (40%)	0.047
No full-term pregnancies	23 (41%)	40 (60%)	
Gynecological history			
PCOS	0 (0%)	1 (1%)	1.0
Endometriosis	1 (2%)	0 (0%)	0.45
Fibroids	5 (9%)	4 (7%)	0.73
Duration of birth control (years)	7.6	8.9	0.18

*p-Value comparing AMH in *BRCA1* positive vs. negative is based on *t*-test comparing the log-transformed values of AMH to adhere to parametric assumptions.

**Patients either declined, it was not observed/asked, or it is unknown.

AMH, anti-Mullerian hormone; BMI, body mass index; PCOS, polycystic ovarian syndrome.

one full-term pregnancy vs. none). Covariates were retained in the logistic model based on significance at the 0.10 level. Models were also fitted with age treated as binary (≤ 35 vs. >35 years of age). Age ≤ and >35 was used as NCCN Guidelines recommend a risk-reducing salpingo-oophorectomy typically between 35 and 40 years, and upon completion of childbearing.

Results

Demographics

A total of 124 patients enrolled in the NOCEDPP met the criteria for our study. Of those, 56 were *BRCA1* and 2 mutation negative and 68 were *BRCA1* mutation positive. The demographic characteristics of this cohort are shown in Table 1. The women with the *BRCA1* mutation were younger ($p=0.001$), less likely to have ever been pregnant ($p=0.048$), and less likely to have had a full-term pregnancy ($p=0.011$) than the women without the *BRCA* mutation. The

distributions of race, current smoking history, obesity, BMI, duration of BC, and gynecological history (including polycystic ovarian syndrome [PCOS], endometriosis, or fibroids) were similar between the groups. Median AMH values in both groups were 2.6 ng/mL (Table 2).

Age, AMH, and *BRCA* mutation status

We examined the association between age and AMH level for *BRCA1* mutation-positive and mutation-negative women. Table 2 shows the AMH values of *BRCA1*-positive and *BRCA1*-negative patients broken down by age groups. The results suggest statistically significant lower AMH scores of *BRCA1*-positive women versus *BRCA1*-negative women over 35. Exploring this relationship further, linear regression results (Fig. 1) demonstrated a negative association between age and AMH in women with *BRCA1* mutation ($p=0.0011$). Among *BRCA1* mutation-negative patients, the association was nonsignificant ($p=0.93$). In addition, we found that the slopes between the two groups were also significantly different ($p=0.028$), indicating a difference between the two groups. It is important to note that in our data set, there was a young (21yo) *BRCA* mutation-negative female with an undetectable AMH (<0.1 ng/mL). When her data were included in the analysis, it altered the slope of the *BRCA* mutation-negative line leading to a still nonsignificant slope in the *BRCA1* mutation-negative women ($p=0.24$), but the comparison of slopes was no longer significant ($p=0.19$).

TABLE 2. MEDIAN ANTI-MULLERIAN HORMONE VALUES IN *BRCA1*-POSITIVE AND -NEGATIVE PATIENTS

	BRCA1-positive	BRCA1-negative
≤ 35	3.1 (n = 23)	3.2 (n = 45)
>35	1.3 (n = 33)	1.8 (n = 23)*

* $p < 0.05$, Wilcoxon rank-sum test.

FIG. 1. Association between age and AMH level by *BRCA1* mutation. Linear regression results demonstrated a negative association between age and AMH in women with *BRCA1* mutation ($p=0.0011$). Among *BRCA1* mutation-negative patients, the association was nonsignificant ($p=0.93$). The slopes between the two groups were also significantly different ($p=0.028$), indicating a difference between the two groups. Of note, there was a young (21yo) *BRCA* mutation-negative female with an undetectable AMH (<0.1 ng/mL), which is denoted by the black circle around her checkpoint. This altered the slope of the *BRCA* mutation-negative line leading to a still nonsignificant slope in the *BRCA1* mutation-negative women ($p=0.24$), but the comparison of slopes was no longer significant ($p=0.19$). AMH, anti-Müllerian hormone.

High versus low AMH

To better understand the association between age and AMH in these two groups, we defined AMH into groups: high AMH defined as $\text{AMH} \geq 0.5$ ng/mL and low AMH as $\text{AMH} < 0.5$ ng/mL (Fig. 2). There was a dramatic difference in the association of high versus low AMH in women with and without the *BRCA1* mutation as seen in Figure 2. The association between low AMH and age was significant for women who were *BRCA1* positive (unadjusted OR=20.2 for a 10 year age difference; $p=0.0028$) and not significant for women who were *BRCA* mutation negative (unadjusted OR=0.98 for a 10 year age difference; $p=0.78$). We found that this difference was statistically significant ($p=0.013$), suggesting strong evidence of a difference in the association of low AMH and *BRCA1* mutation status. Again, the young woman (age 21) with undetectable AMH had a strong influence on the estimates for the *BRCA1*-negative results. Overall inferences remain the same in the *BRCA1*-positive women. However, the comparison of slopes was insignificant when her data were excluded ($p=0.26$) and the estimated unadjusted OR changed to 1.13.

Table 3 shows the distribution of AMH (high vs. low) and age (>35 and ≤ 35) divided by *BRCA* status. Among *BRCA1*-positive women who were >35 years of age, the proportion with low AMH was 0.43. Among *BRCA1*-positive women who were ≤ 35 , the proportion with low AMH was 0.07, yielding an OR of 10.8 ($p=0.001$; 95% confidence interval [CI]: 2.53, 45.9). This means that among *BRCA1*-positive women, women who were >35

years of age had 10 times the odds of low AMH than women ≤ 35 years of age.

Among *BRCA*-negative women, the proportion of women with low AMH in women >35 years of age was 0.09, whereas the proportion among those who were ≤ 35 years of age was 0.17, giving an OR of 0.48 ($p=0.36$; 95% CI: 0.09, 2.41). This suggests that among *BRCA*-negative women, there was not a significant difference in AMH levels when comparing women >35 years of age versus those who were ≤ 35 years of age.

Addressing potential confounders

Logistic regression was performed with low AMH as the outcome to evaluate the association between AMH and potential confounders of the association between AMH and age (Table 4). Longer duration of BC was associated with low AMH in *BRCA*-positive women (OR=3.07 for a 5 year age difference; $p=0.006$). That is, comparing two women who are *BRCA1* positive, one of whom has been on BC for 5 years longer than the other, the woman on BC for 5 years longer had three times the odds of low AMH compared with the other woman. BMI, smoking history, and gravidity did not appear to be related to AMH levels in either *BRCA1* mutation-negative women or positive women. Duration of BC was strongly associated with AMH level in *BRCA1*-positive women and parity was weakly associated with AMH in mutation-positive women. However, neither of those factors was associated with AMH in *BRCA1* mutation-negative women.

FIG. 2. Logistic regression model of high versus low AMH based on *BRCA1* status. The association between low AMH and age was significant for women who were *BRCA1* positive (unadjusted OR=20.2 for a 10 year age difference; $p=0.0028$) and not significant for women who were *BRCA1* mutation negative (unadjusted OR=0.98 for a 10 year age difference; $p=0.78$). This difference was statistically significant ($p=0.013$), suggesting a difference in the association of low AMH and *BRCA1* mutation status. The young woman (age 21) with undetectable AMH had a strong influence on the estimates for the *BRCA1*-negative results. Overall inferences remain the same in the *BRCA1*-positive women, however, the comparison of slopes was insignificant when her data were excluded ($p=0.26$) and the estimated unadjusted OR changed to 1.13. Tick marks along top and bottom of figure represent observed data with tick marks at top being subjects with high AMH who are *BRCA1* mutation positive (solid black) and negative (dotted black). Tick marks along the bottom are those with low AMH who are mutation positive (solid black) and negative (dotted black). OR, odds ratio.

Finally we evaluated gravidity and parity in *BRCA1*-positive versus *BRCA*-negative women. Among *BRCA1*-positive patients, 40% (27/67) had at least one birth. Among *BRCA*-negative patients, 60% (33/56) had at least one birth. This association was significant ($p=0.04$). When evaluating gravidity, the association was also significant. Among *BRCA1* positives, 43% had at least one pregnancy and among *BRCA1* negatives, 68% had at least one pregnancy ($p=0.0071$).

Based on logistic regression results presented in Tables 3 and 4, significant predictors ($p<0.10$) were included in a multiple logistic regression model. As can be seen from Table 5, after adjusting for parity and duration of BC, age was still strongly associated with low AMH. The effect was attenuated (adjusted OR=5.64), but still remained significant ($p=0.03$).

Discussion

Young women carrying the *BRCA1* or *BRCA2* mutation are faced with many decisions regarding their reproductive health and childbearing future. This study indicates that women who are *BRCA1* mutation positive may have a significant decline in AMH levels, especially after age 35. We found that women with the *BRCA1* mutation >35 years of age had a 10 times higher odds of a low AMH than women ≤ 35 years of age. This is especially important when we consider the fact that women are waiting longer to start families. Recent CDC data indicated that the rate of first birth in women aged 35–39 has increased six-fold from 1973 to 2012. Additionally, the average age of first birth has increased by 3.6 years between 1973 and 2006 and continues to rise.^{22,23} We did not observe a decline in AMH in the *BRCA*-negative

TABLE 3. DISTRIBUTION OF ANTI-MULLERIAN HORMONE AND AGE PER *BRCA* MUTATION STATUS

	<i>BRCA1-positive</i>			<i>BRCA-negative</i>		
	<i>AMH</i>			<i>AMH</i>		
	<i>Low</i>	<i>High</i>	<i>Total</i>	<i>Low</i>	<i>High</i>	<i>Total</i>
Age >35	10 (43%)	13 (57%)	23	3 (9%)	30 (91%)	33
Age ≤ 35	3 (7%)	42 (93%)	45	4 (17%)	19 (83%)	23
Total	13	55	68	7	49	56

TABLE 4. ASSOCIATIONS BETWEEN COFOUNDERS AND BRCA STATUS

Covariate	Odds ratio (p-value) in BRCA- negative women	Odd ratio (p-values) in BRCA- positive women	p-Value testing difference in BRCA pos vs. neg
BMI (5 U difference)	0.85 (0.70)	0.99 (0.97)	0.79
Duration of birth control (5 years increment)	0.77 (0.50)	3.07 (0.006)	0.015
Smoking (ever)	1.78 (0.53)	2.61 (0.18)	0.74
Gravidity (>0 vs. 0)	1.21 (0.83)	2.51 (0.15)	0.50
Parity (>0 vs. 0)	0.92 (0.92)	2.95 (0.09)	0.26

Results are from simple logistic regression models.

group; however, this was likely due to the fact that there was not a wide age span among this group.

Other studies have found that smoking is associated with an increased decline in AMH with age compared with non-smokers. We found no relation to smoking history and risk of a decline in AMH. This is likely because of the low number of smokers in this study. In this cohort, the incidence of a current smoking history was 1% ($n=1$) in the BRCA-negative group and 6% ($n=4$) in the BRCA1-positive group. Previous studies had also demonstrated that natural menopause appears to occur up to 3 years earlier in smokers.^{24,25} The mechanism behind this association is likely related to the toxic effect of smoking on ovarian follicular depletion and may lead to diminished ovarian reserve at earlier reproductive years.²⁴

Obesity was evaluated as a covariate, but had no significant association with a decline in AMH in our study. There are conflicting reports of the associations between obesity and AMH,^{18–20,26} thus the association remains open to scrutiny.

In this study, duration of BC was associated with a lower AMH in BRCA1 mutation women. Previous studies reported similar findings and demonstrated that women taking BC

may have a lower AMH and fewer early stage follicles than women who do not take BC. In previous studies these effects were seen even after adjusting for both smoking history and BMI.²⁷

In our study, there was a significant association between both gravidity and parity and BRCA mutation status. Among BRCA1 mutation-positive women, 43% had at least one pregnancy versus 68% of BRCA mutation-negative women ($p=0.0071$). A similar association was seen with births. Among BRCA1 mutation-positive women, 40% had at least one term birth versus 60% of BRCA mutation-negative women ($p=0.04$). Previous studies looking at the BRCA mutation and reproduction had differing results. As mentioned in the introduction, one case-control study examined 2,254 BRCA carriers and 764 noncarrier controls from the same families and found little to no effect of the BRCA gene mutation on parity and fertility.¹⁰

In our multivariable analysis, where we considered potential confounding variables, including BMI, duration of BC, smoking, gravidity, and parity, we found that >35 years of age was still strongly associated with a low AMH in BRCA1 mutation-positive women (OR = 5.64; $p=0.03$).

To our knowledge, there are two relevant studies comparing AMH levels in BRCA carriers and controls. One study by Michaelson-Cohen et al. tested 41 healthy BRCA1/2 mutation carriers, ages 26–40 years, for AMH levels and compared levels with those of their general population.²⁸ They concluded that AMH levels of healthy BRCA 1/2 mutation carriers are similar to those of noncarrier women matched for age. However, this study was limited by its small sample size and did not analyze BRCA1 and BRCA2 carriers separately, which may explain the difference in our findings. A study by Wang et al. evaluated AMH levels in 143 women who underwent genetic testing for BRCA deleterious mutations due to a family history of cancer.²⁹ This study included women with either the BRCA1 or BRCA2 mutation. Although this study reported results similar to ours in terms of an association between BRCA1 mutation status, age, and AMH levels, there are significant differences in our study and theirs. First, their study did not report an association with BRCA mutation status and gravidity or parity. If fertility is truly impaired in BRCA1 mutation carriers, one would expect to see a correlating decline in pregnancies and live births in the BRCA1 population as well. Small and specific subsets of women used in these studies may be an explanation for this difference. Another difference between this study and our study is that oral contraception data were not collected for all women in their study and was, therefore, not accounted for in the regression model.

The findings in our study from otherwise healthy women may not be applicable to women with menstrual cycle irregularities, other gynecological issues, including PCOS and endometriosis, or other health problems. In our study set, there was only one woman with PCOS and one woman with endometriosis, making it impossible to draw a conclusion regarding the associations with these gynecological conditions. However, it is possible that these conditions play a role in ovarian reserve. Other limitations to consider are differences in the AMH assays. Because of this, caution should be taken when comparing AMH levels between studies. There was also little variation in race with 72% of our study population reported as white.

TABLE 5. MULTIPLE LOGISTIC REGRESSION RESULTS FOR ASSOCIATION BETWEEN AGE AND ANTI-MULLERIAN HORMONE, ADJUSTED FOR DURATION OF BIRTH CONTROL AND PARITY

Covariate	Odds ratio (p-value) in BRCA- negative women	Odds ratio (p-values) in BRCA- positive women	p-Value testing difference in BRCA pos vs. neg
Age (>35)	0.41 (0.36)	5.64 (0.03)	0.037
Duration of BC (5 years increment)	0.77 (0.55)	2.20 (0.05)	0.074
Parity	1.75 (0.56)	1.82 (0.43)	0.97

Outcome is low AMH versus high AMH.
BC, birth control.

This study suggests a significant decline in ovarian reserve in *BRCA1* mutation carriers >35 years of age. Further research, including a larger prospective study following both *BRCA*-positive and negative women over time, is needed to confirm the reliability and clinical utility of these results. Having lower ovarian reserve would place these women at a higher risk for chemotherapy-induced ovarian failure. In addition, this is critical information for the counseling of these women when faced with making decisions about family building, fertility preservation, as well as future fertility.

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