

**Review Article**

## **Association between BRCA 1, BRCA 2 and Ovarian Reserve: Current Evidence and Future Possibilities via a Review of the Literature**

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### **Abstract**

A great amount of studies had shown already that BRCA 1 and BRCA 2 mutations are related with breast and ovarian cancer. BRCA1 plays an important role in maintaining genome integrity, at least in part, through its roles in DNA damage repair. DNA damage can happen in both single-strand DNA breaks and double-strand DNA breaks (DSBs). Because DSBs can affect both copies of a gene, they can result in mutagenesis,

carcinogenesis, cell senescence, or apoptotic cell death. BRCA1 and BRCA2 genes belong to the family of ataxia-telangiectasia-mutated (ATM)-mediated DNA DSB repair genes. It plays a critical role in the safeguarding of DNA integrity. Some studies showed that DSBs accumulate with age and contribute to reproductive aging in mice and women. It was observed that females with BRCA mutations, undergoing fertility preservation, have lower response rates to ovarian

stimulation. Furthermore, some studies came to the conclusion that females with BRCA mutations may have earlier menopause compared with non-carriers. The results vary and we cannot have a solid answer if BRCA1 and BRCA2 mutations play a significant role in the ovarian reserve. The majority of the studies with sufficient sample size and/or which are prospective in nature, supports that ovarian reserve is decreased in women with BRCA1 mutations, although not all the studies agreed with this conclusion. The aim of this work is to review the literature pertaining to this issue.

**Keywords:** BRCA 1 Mutations; BRCA 2 Mutations; Breast Cancer; Ovarian Cancer; Ovarian Reserve

## 1. Introduction

The breast cancer associated gene 1 (BRCA1) was mapped in 1990 [1] and cloned four years later [2]. Mutations of BRCA1 predispose women to ovarian and breast cancer [3]. BRCA1 plays an important role in maintaining genome integrity, at least in part, through its roles in DNA damage repair. In a single human cell, more than 10,000 lesions take place per day but due to continuous DNA repair mechanisms, an organism's life span is generally not affected [4]. DNA damage can happen in both single-strand DNA breaks and double-strand DNA breaks (DSBs). Because DSBs can affect both copies of a gene, they can result in mutagenesis, carcinogenesis, cell senescence, or apoptotic cell death [5]. BRCA1 and BRCA2 genes belong to the family of ataxia-telangiectasia-mutated (ATM)-mediated DNA DSB repair genes. It plays a critical role in the safeguarding of DNA integrity. BRCA mutation not only increase the risk of ovarian and breast cancer especially prior to menopause but also increases the risk for other types of malignancies such as melanoma, prostate cancer and pancreatic cancer [6]. Increasing

evidence shows that mutations in other DNA repair genes are linked to breast and other cancer types [7]. Most of families with many different cases of breast and ovarian cancer have inherited mutations in BRCA1 and BRCA2 [8-10]. The cumulative life-time risks of ovarian cancer related with these genes was around 40–53% for a BRCA1 mutation carriers and 20-30% in BRCA2 carriers, although, these risk estimates appear to differ between researches [11, 12].

## 2. Ovarian Reserve

Poor ovarian reserve (POR) shows a decrease in the quantity of ovarian follicular pool in women of reproductive age group. As we already know, fertility peaks before the age of thirty and thereafter, it is decreased gradually. This is because of a decrease in primordial follicular due to continuous ovulation and follicular atresia. It is believed that there is progressively increasing rate of atresia throughout the reproductive period [13]. There is also variation in the size of the non-growing follicular (NGF) pool between females. Even among those with “normal ovarian reserve” of the same age, the variation in the size of the follicular pool can be as high as 100-fold [13]. Recognizing POR, whether age-related or not, is crucial because these females have a decrease pregnancy rate but also, they have higher pregnancy loss compared with females that have normal ovarian reserve [14]. Shortening of the menstrual cycles due to early follicle development and ovulation is an indicator of POR [15]. Females have a limited number of germ cells whose number peaks at 6–7 million by gestation week 20. From mid-gestation onward and during reproductive life, an irreversible attrition progressively decreases the germ cell pool of the gonad [16]. From all the ovarian reserve tests that are used nowadays, the two most commonly used are AMH (AntiMullerian Hormone)

and AFC (Antral Follicle Count). A typical AMH level for a fertile woman is 1.0–4.0 ng/ml; under 1.0 ng/ml is considered low and indicative of a diminished ovarian reserve. Females with BRCA mutations, undergoing fertility preservation, have lower response to ovarian stimulation and these specific mutations could be related to ovarian aging [17] and earlier menopause.

### 3. Results

Different studies took place over the past years to find out if there is any relationship between BRCA1 and BRCA2 and ovarian reserve. The amount of studies is still limited. Wang et al made an analysis with 143 women, of whom 62 were BRCA1 carriers, 27 were BRCA2 carriers, and 54 were controls [18]. There were significant differences of AMH levels between BRCA1 carriers and controls ( $P=0.026$ ) but not between BRCA2 carriers and controls ( $P=0.470$ ) nor between BRCA1 and BRCA2 carriers ( $P=0.634$ ). It was concluded that BRCA1 carriers have lower age- and body mass index (BMI)-adjusted serum AMH levels compared with women without BRCA mutations. Another research by Titus et al showed that double-stranded breaks (DSBs), accumulate with age and contribute to reproductive aging in mice and women [19]. In mouse and human oocytes, the expression of some DSB repair genes (*BRCA1*, *MRE11*, *RAD51*, and *ATM*) decreases with age. So, in the oocyte genome we have the accumulation of DSBs because of age-related missteps in DSB repair, which stimulate apoptosis and decreases ovarian reserve. BRCA1 gene expression showed an important age-related decrease ( $P < 0.001$ ). On the other hand BRCA2 gene expression did not show a correlation with age in the same oocytes ( $P = 0.75$ ). In another study Oktay et al showed that BRCA mutations negatively affect ovarian reserve [20]. They found that with the increase of female's age it is also more likely to

accumulate DNA DSBs in their oocytes. To find out if DNA DSB repair efficiency decreases with age, they collected immature oocytes of women age between 21 and 43 with non-ovarian infertility, and quantified expression of key ATM-mediated DNA DSB repair genes including BRCA1, BRCA2, ATM, MRE11 and Rad51. Notably, expression of all but the BRCA2 gene decreased with age. This decrease was more prominent after age 36 [19]. They measured also serum AMH levels and they found out that women with BRCA1 mutation had a decrease in AMH levels compared with BRCA mutation negative females with breast cancer. Although this decrease was not happening in females with BRCA2 mutations [19]. In a research that took place in Australia and New Zealand, Phillips et al included 1636 families, started on 1997 and is ongoing [21]. 693 people were involved in the study sample, involving 172 carriers with BRCA1 mutation, 216 women who were negative for BRCA1 mutation, 147 carriers with BRCA2 mutation and 158 who were negative for BRCA2. As a result of this research BRCA1 mutation carriers had 25% lower AMH concentrations than non-carriers. There was no clue that this relation varied with age ( $P$ -interaction 0.61). There was no important difference in average AMH concentrations between BRCA2 mutation carriers and non-carriers. In a study that took place in South Korea 316 patients included, 264 were BRCA-negative and 52 were BRCA-positive (27 BRCA1-positive and 25 BRCA2-positive) [22]. Patients with any BRCA mutation had a significantly lower median AMH than those without a mutation (2.60 vs. 3.85 ng/mL,  $P = 0.004$ ). Serum AMH levels of the BRCA1 (2.56 ng/mL,  $P = 0.001$ ) and BRCA2 groups (2.64 ng/mL,  $P = 0.036$ ) were significantly lower than that of BRCA-negative group, but no difference was found between the BRCA1 and BRCA2 groups [22]. Also in a research by Irit Ben-

Aharon et al they measured AMH levels in both BRCA-carriers and non carriers to find if there is a decrease in the ovarian reserve but also they calculated other biomarkers such as IL-1 (Interleukin-1), FGF-23 (fibroblast growth factor-23 ) to see if BRCA mutation is related with systemic aging [23]. The concentration of IL-1 and FGF-23 is increased with aging. FGF-23 was higher in BRCA carriers of both genders than in the control group (P=0.06), also IL-1 was higher in carriers than in control group but there was not a statistical significance. This research may show a connection not only between BRCA mutation and gonadal aging but also with systemic aging [23].

In contrast, not all the studies agreed that there is a relation between BRCA1 and ovarian reserves. In a study that took place by Johnson et al. they included 213 subjects [24]. The analysis involved females younger than 40 years old with regular menses. AMH levels were 33% lower in BRCA2 carriers compared with low-risk control women. BRCA1 carriers had AMH levels similar to low-risk control women in all models. Van Tilborg et al included 255 women aged 18–45 years, with a familial BRCA1/2 mutation, [25]. In this study no data was found for an association between BRCA1/2 mutation status and a decrease quantitative ovarian reserve, when assessed by serum AMH levels. Also in another study that took place in Canada and United States by Pal T et al. they found that there is likely little or no effect of the BRCA gene mutation on fertility [26]. They found 764 matched sets for the analysis (566 BRCA1, 194 BRCA2, 4 both). They found 1,100 carriers with a previous history of breast cancer (48.8%). Because of overall parity being similar between carriers and non-carriers, there is likely little or no effect of the BRCA gene mutation on fertility.

#### 4. BRCA1, BRCA2 Mutation And Earlier Menopause

A poor response to ovarian stimulation during IVF has been related with early menopause [27, 28]. Collins et al did a research to find if BRCA1 and BRCA2 mutation carriers have earlier natural menopause than their non-carrier relatives [29]. This research by Collins involved 445 carriers of BRCA1 mutation, 559 women who were negative for this mutation in their family, 374 carriers of BRCA2 mutation, and 462 women who were negative for BRCA2 mutation. This specific research found no evidence that BRCA1 and BRCA2 mutation carriers had earlier menopause compared with non-carrier relatives, however the study was limited by the fact that only 19% of the sample reached natural menopause [29]. In another research by Rzepka-Gorska et al found an important variation in age at menopause between BRCA1 carriers and non-carriers after treatment for breast cancer, with a mean age at menopause 1.9 years earlier for mutation carriers [30]. Moreover, in a study that took place in California by Lin et al found that BRCA1 and BRCA2 were related with a significantly earlier age at natural menopause and heavy smoking compounded this risk [31]. A total of 537 female BRCA1/2 carriers were found, and 382 (238 with BRCA1 and 144 with BRCA2) were white [31]. Between the SWAN (Study of Women's Health Across the Nation) participants, 765 were classified as living in northern California and as being white. The conclusion of this research was that the BRCA1/2 mutation carrier was associated with undergoing natural menopause 3 years to 4 years earlier than was noted in a community sample of midlife white women

In another one in USA and Canada by Finch et al tried to assess the result of having a BRCA1 or BRCA2 mutation [32]. They found 908 women with BRCA1 or BRCA2 mutation and paired them with women who did

not have this mutation. Finch et al found that age of menopause was lower for BRCA-positive women comparing with BRCA-negative (49.0 vs. 50.3 years; P 0.001). This was accurate for both BRCA1 and BRCA2 carriers. To evaluate the amount of females who underwent early menopause, they checked which of these females reaches menopause before age 40 and before age 45 years. They discovered that a higher amount of BRCA-positive females had entered menopause before age 40 years compared with non-carrier control subjects (4.7% vs. 1.4%; P 0.04). The variation in very early menopause was about quadruple and affected 5% of the carrier population. It is possible that some of these females were subfertile for a decade before reaching menopause [32].

## 5. Discussion

As we can see the results vary and we cannot have a solid answer if BRCA1 and BRCA2 mutation play a role in the ovarian reserve. The majority of the studies with sufficient sample size and/or which are prospective in nature, supports that ovarian reserve is decreased in women with BRCA1 mutations. On the other hand, some researchers such as Johnson et al found a relation between BRCA2 and ovarian reserve. Some other studies found no relation at all. A possible explanation why the results differ in some studies is that they took different criteria. A typical example is the race of the cohorts. Some of them are from Canada others are African-Americans, others, Caucasian and some others from Australia and New Zealand. Another reason that the results can vary is the blood samples. In some of the studies the blood samples were randomly selected during the menstrual cycle, though conflicting results have been reported concerning intra-cycle variability of AMH levels. Possible changes that is created by random blood sampling may have affected the association

among groups and may have limited the discovery of small but clinically unimportant variations. Also not all studies took the same amount of women with BRCA1, 2 mutations. Some of the studies took many years to happen with big amount of samples while the other had only a small amount of females. Another significant preference that may hinder the exposure of quickened ovarian aging in women with BRCA mutations is the elimination of the most seriously affected people from a study group due to earlier risk reducing salpingo-oophorectomy (RRSO), ovarian cancer, premature ovarian failure, and chemotherapy for breast cancer. This initial reduction of difficult cases of BRCA dysfunction would give the uninfluenced and least influenced people for analysis in a general BRCA mutation population. Also, hormonal contraceptives, age, smoking, and menstrual irregularity (some studies involve those women while others not) can affect the final result. Furthermore, researches that target unaffected carriers may miss any small effect of BRCA mutations, as the diminish in the role of the intact BRCA gene may be less meaningful in unaffected females.

## 6. Conclusion

As we can see in this review, there seems to be a relationship between the BRCA gene function, intact DNA DSB repair function and the maintenance of ovarian reserve. Females with BRCA1 mutations may have lower ovarian reserve in reproductive age. In general, it is not so easy to see an effect of BRCA mutations on fertility in the early reproductive years. It is suggested that BRCA positive women without cancer who are older than 35 years and wish to have children may consider a consultation with a fertility specialist. BRCA1/2 carriers may have a narrower reproductive window than non-carriers. So, in addition to discussing risk-reducing salpingo-oophorectomy, we would



encourage the early initiation of fertility counseling for BRCA1/2 carriers and the consideration of earlier childbearing. More researches with adequate sample size are needed to verify the preexisting data to see if BRCA mutations result in accelerated reproductive aging and premature infertility. Further researches analyzing the association between BRCA function, DNA repair mechanisms and oocyte quality are also required.

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