

UC Davis

UC Davis Previously Published Works

Title

Association of Germline BRCA Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data

Permalink

<https://escholarship.org/uc/item/9r726877>

Journal

Journal of Clinical Oncology, 39(18)

ISSN

0732-183X

Authors

Turan, Volkan
Lambertini, Matteo
Lee, Dong-Yun
et al.

Publication Date

2021-06-20

DOI

10.1200/jco.20.02880

Peer reviewed

Association of Germline BRCA Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data

Volkan Turan, MD^{1,2}; Matteo Lambertini, MD^{3,4}; Dong-Yun Lee, MD⁵; Erica Wang, MD⁶; Florian Clatot, MD⁷; Beth Y. Karlan, MD⁸; Isabelle Demeestere, MD⁹; Heejung Bang, PhD¹⁰; and Kutluk Oktay, MD, PhD^{1,11}

PURPOSE To determine whether germline *BRCA* (*gBRCA*) pathogenic variants are associated with decreased ovarian reserve.

MATERIALS AND METHODS An individual patient-level data meta-analysis was performed using five data sets on 828 evaluable women who were tested for *gBRCA*. Of those, 250 carried *gBRCA*, whereas 578 had tested negative and served as controls. Of the women with *gBRCA*, four centers studied those affected with breast cancer ($n = 161$) and one studied unaffected individuals ($n = 89$). The data were adjusted for the center, age, body mass index, smoking, and oral contraceptive pill use before the final analysis. Anti-Müllerian hormone (AMH) levels in affected women were drawn before presystemic therapy.

RESULTS The mean age of women with versus without *gBRCA1/2* (34.1 ± 4.9 v 34.3 ± 4.8 years; $P = .48$) and with *gBRCA1* versus *gBRCA2* (33.7 ± 4.9 v 34.6 ± 4.8 years; $P = .16$) was similar. After the adjustments, women with *gBRCA1/2* had significantly lower AMH levels compared with controls (23% lower; 95% CI, 4 to 38; $P = .02$). When the adjusted analysis was limited to affected women (157 with *gBRCA* v 524 without, after exclusions), the difference persisted (25% lower; 95% CI, 9 to 38; $P = .003$). The serum AMH levels were lower in women with *gBRCA1* (33% lower; 95% CI, 12 to 49; $P = .004$) but not *gBRCA2* compared with controls (7% lower; 95% CI, 31% lower to 26% higher; $P = .64$).

CONCLUSION Young women with *gBRCA* pathogenic variants, particularly those affected and with *gBRCA1*, have lower serum AMH levels compared with controls. They may need to be preferentially counseled about the possibility of shortened reproductive lifespan because of diminished ovarian reserve.

J Clin Oncol 39:2016-2024. © 2021 by American Society of Clinical Oncology

INTRODUCTION

BRCA1 and *BRCA2* (*BRCA1/2*) play an essential role in double-strand DNA break (DSB) repair through recombination with undamaged, homologous DNA strands.¹ Mutations in these genes are associated with increased susceptibility to breast and ovarian cancer.² Starting with our first clinical and laboratory observations,³⁻⁷ a growing body of laboratory, translational, and clinical evidence has emerged within the last decade, indicating a role for *BRCA* and related DNA DSB repair genes in ovarian function and aging.^{6,7}

Anti-Müllerian hormone (AMH) is the best available serum marker of ovarian reserve. It is produced by granulosa cells of small antral and preantral follicles in the ovary and, by proportion, reflects the primordial follicle reserve.⁸ Serum AMH levels do not significantly fluctuate and can be measured at any point during the menstrual cycle. In contrast, the levels of indirect and less sensitive ovarian reserve markers such as follicle-

stimulating hormone and E2 are highly dependent on the menstrual cycle day. One limitation for all ovarian reserve markers is that their levels can be affected by smoking, oral contraceptive use, and obesity.⁹ Several studies have used serum AMH to investigate whether germline *BRCA* (*gBRCA*) pathogenic variants are associated with diminished ovarian reserve. Although a majority of studies indicated diminished ovarian reserve in women with *gBRCA1/2*, some provided conflicting results.⁵⁻¹⁹ Several clinical studies including our own⁵ and transgenic mouse data indicated a stronger association of *gBRCA1* with diminished ovarian reserve than with *gBRCA2*; however, one study found *gBRCA2* but not the *gBRCA1* to be associated with lower ovarian reserve.¹⁵ Several other studies did not detect lower serum AMH levels in women with *gBRCA* compared with controls.^{14,18,19}

We recently performed a systematic review to investigate the role of *gBRCA* in ovarian aging.⁶ We found that the small sample size, lack of adjustment for important covariates (such as age, smoking, and oral

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 9, 2021 and published at ascopubs.org/journal/jco on April 23, 2021; DOI <https://doi.org/10.1200/JCO.20.02880>

CONTEXT

Key Objective

Deoxyribonucleic acid repair deficiency is emerging as a joint mechanism for breast cancer and reproductive aging. Recent studies showed that ovarian reserve may be lower in women with *BRCA* (*gBRCA*) pathogenic variants because of deoxyribonucleic acid repair deficiency. However, clinical studies using the most sensitive serum ovarian reserve marker anti-Müllerian hormone provided mixed results. Given the heterogeneity of the data from clinical studies, we performed an individual patient data meta-analysis to determine if *gBRCA* is associated with lower ovarian reserve.

Knowledge Generated

gBRCA is associated with diminished ovarian reserve, as determined by serum Anti-Müllerian hormone, and this association seems to be restricted to *gBRCA1*. This finding is firmer for affected women as this individual patient data meta-analysis predominantly studied those with breast cancer.

Relevance

Women with *gBRCA* may have shortened reproductive life span because of diminished ovarian reserve and should be proactively counseled for fertility preservation especially if faced with chemotherapy or delaying childbearing.

contraceptive pill use), not accounting for differences between the *gBRCA1* and *gBRCA2* carriers, and inadequate statistical methods were among the major limitations of many studies investigating the association between *gBRCA* and serum AMH levels. To address these limitations and to provide more conclusive clinical assessment of this critical topic, we performed an individual patient-level data (IPD) analysis with studies that investigated serum AMH levels in women with *gBRCA1/2*.

Based on laboratory⁵ and clinical data,⁶ we hypothesized that AMH levels are lower in women with *gBRCA1/2*, especially in those carrying *gBRCA1*, compared with the individuals who tested negative for *gBRCA1/2*. To that end, we report the comparison of serum AMH levels in women with *gBRCA1/2* compared with those who were found to be negative for mutations in the same genes.

MATERIALS AND METHODS

We searched for published articles in the PubMed database containing keywords, *BRCA*, *BRCA1*, *BRCA2*, mutations, *BRCA pathogenic variants*, ovarian reserve, and AMH in the English-language literature until December 2019. We found 12 original studies investigating the association between *gBRCA1/2* and serum AMH levels, four of which included only affected women with breast cancer^{5,10,20,21} and one included both affected and unaffected¹⁸ (Data Supplement, online only). After the study was approved by the Institutional Review Board (TR21092018/025), invitation letters were sent to all corresponding authors of the published articles. Four centers declined to participate, and three did not respond. Of the seven nonparticipating centers, all studied unaffected women with the exception of one, which also included a small contingent of affected women. Five centers shared their IPD from their publications. In addition, Lambertini et al¹⁰ updated their data with additional cases. In their

published manuscript, the numbers of women with and without *gBRCA1/2* were 25 and 60, respectively. After updating their data, these numbers reached 50 and 85, respectively. As a result, a meta-analysis with five centers using IPD with some common key variables was conducted. Of those five centers, four (centers from New York, South Korea, Belgium, and France) studied women affected with breast cancer. One center studied unaffected women (Los Angeles, CA).

Data Collection and Inclusion and Exclusion Criteria

For all participants enrolled in each of the included studies, IPD that contained demographics, parity, smoking status, oral contraceptive pill use, the *gBRCA1* and/or *gBRCA2* testing status, breast cancer stage (if affected), and serum AMH levels were collected. In affected women, serum AMH was drawn before the initiation of chemotherapy.

The common inclusion criteria were age 18–45, premenopausal status, no prior or ongoing chemotherapy or pelvic surgery, no use of endocrine therapy, and having been tested for *gBRCA1/2*. Other than one center (Los Angeles, CA), all excluded women with irregular periods and history of polycystic ovarian diseases or other reproductive endocrine disorders.

AMH Assessment

Statistics. We summarized patient characteristics by *gBRCA* status using standard descriptive statistics—mean and standard deviation (SD) for continuous variables and frequency and proportion for categorical variables. We set 0.01 as the detection limit and used log₁₀-transformed AMH data following our previously published approach²² and our examination of the AMH data for this IPD meta-analysis.

Data were analyzed using the statistical methods for multicenter studies or IPD meta-analysis with patient-level covariates and outcomes.^{23–25} The age-adjusted model was

fit for five studies or centers individually, and sequentially adjusted models (from center and age only to center, age, smoking, oral contraceptive pill use, and body mass index [BMI]) for the combined sample. Smoking and oral contraceptive pill (OCP) use were categorized to three levels (Y, N, and missing) to avoid imputation and to use maximum sample size. Patients with missing BMI (as continuous variable) were not included when BMI was adjusted, ie, we did not impute missing continuous variables, including BMI. Fixed effects (FE) models were chosen as the primary method as explained in the Data Supplement.

The primary exposure of interest was *gBRCA* status (Y/N). In the secondary analysis, three levels of *gBRCA* type 1 versus *gBRCA* type 2 versus negative (as reference group) were considered. We analyzed data using SAS 9.4 (SAS Institute, Cary, NC). AMH differences in each study and pooled version were visualized in a forest plot.

RESULTS

General Description of the Study Population

After excluding four women with variance of unknown significance in *BRCA*, a total of 824 of 828 women were

eligible for the final analysis (Fig 1). Two hundred and forty-six women tested positive for *gBRCA1/2*, and 157 (78.5%) of those were affected with breast cancer. Eighty-nine women with *gBRCA* were unaffected. Of the 246 women with *gBRCA*, 153 (62.2%) were positive for *gBRCA1*, whereas 93 women (37.8%) for *gBRCA2*. Among the mutation negative controls ($n = 578$), 524 were affected with breast cancer.

Women with and without *gBRCA* had similar age at study inclusion compared with noncarrier controls (mean \pm SD, 34.1 ± 4.9 v 34.3 ± 4.8 years, respectively; $P = .48$). The demographic characteristics of the entire or combined sample are summarized in Table 1.

Comparison of Serum AMH Levels in Women With and Without *gBRCA1/2*

The mean AMH level in women with *gBRCA1/2* was 2.04 ng/mL (SD = 2.0, median of 1.5, and geometric mean of 0.99), whereas it was 3.36 ng/mL (SD = 3.1, median of 2.5, and geometric mean of 1.96) in women without mutations. After adjusting for center, age, smoking status, and OCP use, women with *gBRCA* had significantly lower AMH levels compared with those without (26% lower [95% CI, 4

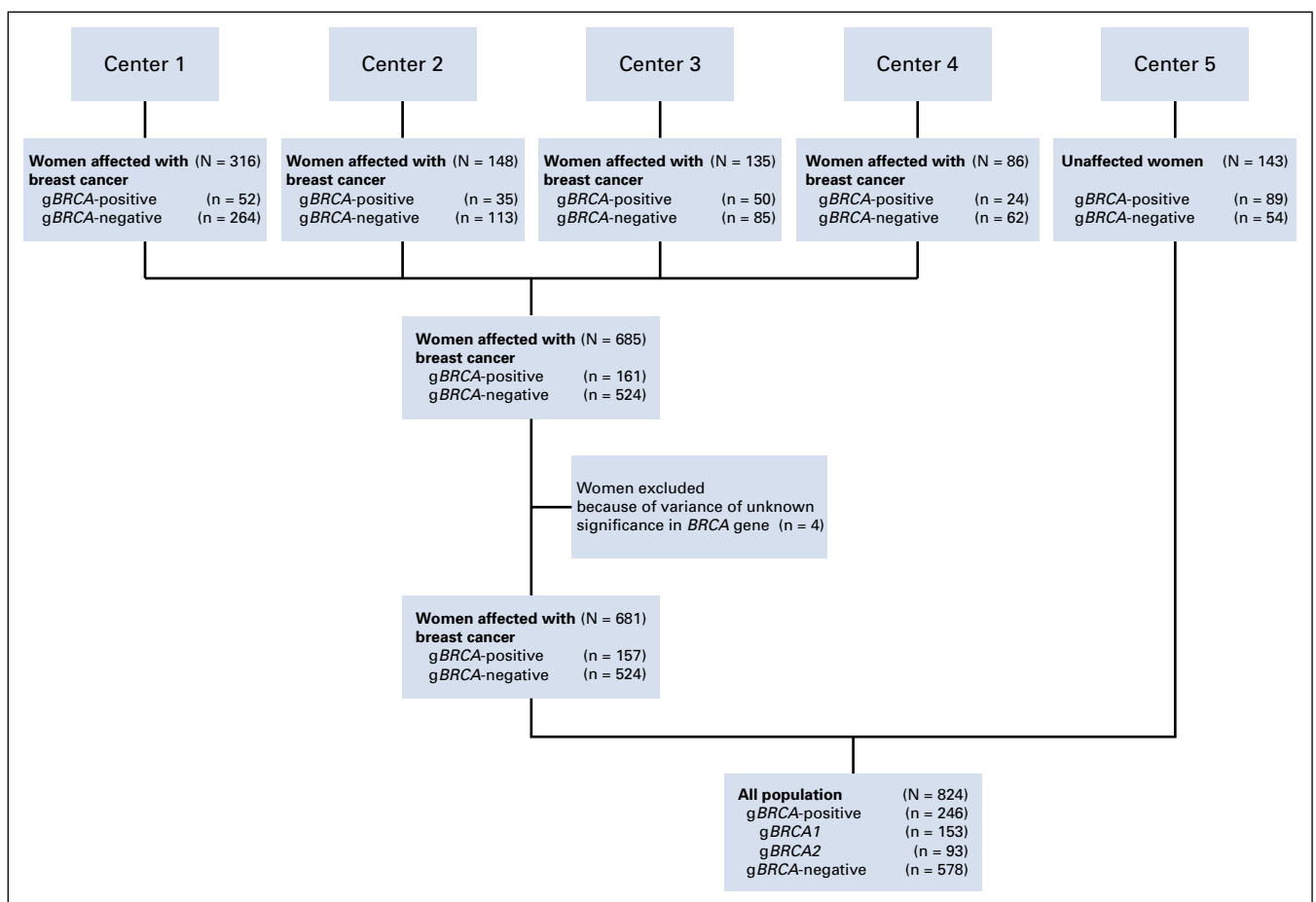


FIG 1. Study inclusion and exclusion flowchart.

TABLE 1. Population Characteristics

Characteristic	<i>gBRCA</i> -Positive (N = 246)	<i>gBRCA</i> -Negative (N = 578)
Age at blood sample (years), mean ± SD	34.1 ± 4.9	34.3 ± 4.8
BMI (kg/m ²), mean ± SD	n = 201 23.0 ± 4.5	n = 519 22.7 ± 4.2
Parity, No. (%)		
Yes	126 (51.2)	215 (37.2)
No	120 (48.8)	264 (45.7)
Missing	0 (0)	99 (17.1)
<i>BRCA</i> mutation type, ^a No. (%)		
<i>gBRCA1</i>	153 (62.2)	NA
<i>gBRCA2</i>	93 (37.8)	
Breast cancer, No. (%)		
Yes	157 (63.8)	524 (90.6)
No	89 (36.2)	54 (9.3)
Stage, No. (%)		
I and II	77 (49.0)	340 (64.8)
III and IV	48 (30.5)	119 (22.7)
Unknown	32 (20.3)	65 (12.4)
OCP use, No. (%)		
Yes	54 (22.0)	97 (16.8)
No	159 (64.6)	430 (74.4)
Missing	33 (13.4)	51 (8.8)
Smoking, No. (%)		
Yes	33 (13.4)	63 (10.9)
No	164 (66.7)	437 (75.6)
Missing	49 (19.9)	78 (13.5)

Abbreviations: BMI, body mass index; NA, not available; OCP, oral contraceptive pills; SD, standard deviation.

^aFour cases of variants of unknown significance in *BRCA1/2* were excluded.

to 38]; $P = .004$). After the inclusion of BMI in the adjusted model, the sample size was reduced because of the missing data (from 824 to 720; Table 2), but qualitatively similar results were observed; for example, we found 23% decrease in AMH (95% CI, 4 to 38; $P = .02$) for *gBRCA1/2* carriers versus noncarriers (Fig 2 and Table 2).

Comparison of Serum AMH Levels in Women With *gBRCA1* Versus *gBRCA2* With Controls

To further evaluate whether there was a difference in ovarian reserve according to type of *gBRCA*, we categorized women into those with *gBRCA1*, *gBRCA2*, and no mutations. The comparison among these three groups showed that the AMH levels were significantly lower in women with *gBRCA1* compared with controls after adjusting for age, smoking, and OCP use with (33% lower; $P = .004$) or without (35% lower; $P = .0004$) adjustment for BMI (Table 3). A similar comparison of AMH levels between the women with *gBRCA2* and controls did not

reveal a difference; 7% lower ($P = .64$) and 9% lower ($P = .52$), respectively (Table 3).

Comparison of Serum AMH Levels in Affected (Breast Cancer) Women With and Without *gBRCA*

It is possible that the *BRCA* dysfunction is more severe in affected women with mutations, and hence, the ovarian reserve may be more severely compromised in the same group. Therefore, we repeated our analysis by excluding the data from center 5 ($n = 143$), which studied unaffected women with and without *gBRCA*. Of the remaining 681 women with a new diagnosis of breast cancer, 91 had *gBRCA1*, 66 had *gBRCA2*, and 524 tested negative for *gBRCA1/2* (Tables 2 and 3).

The mean age of 157 and 524 affected women with and without *gBRCA1/2* was 33.3 ± 4.3 and 33.8 ± 4.5 years, respectively ($P = .18$). The mean AMH level was 2.54 ng/mL (SD = 2.3, median of 1.9, and geometric mean of 1.66) in affected women with *gBRCA*, whereas it was

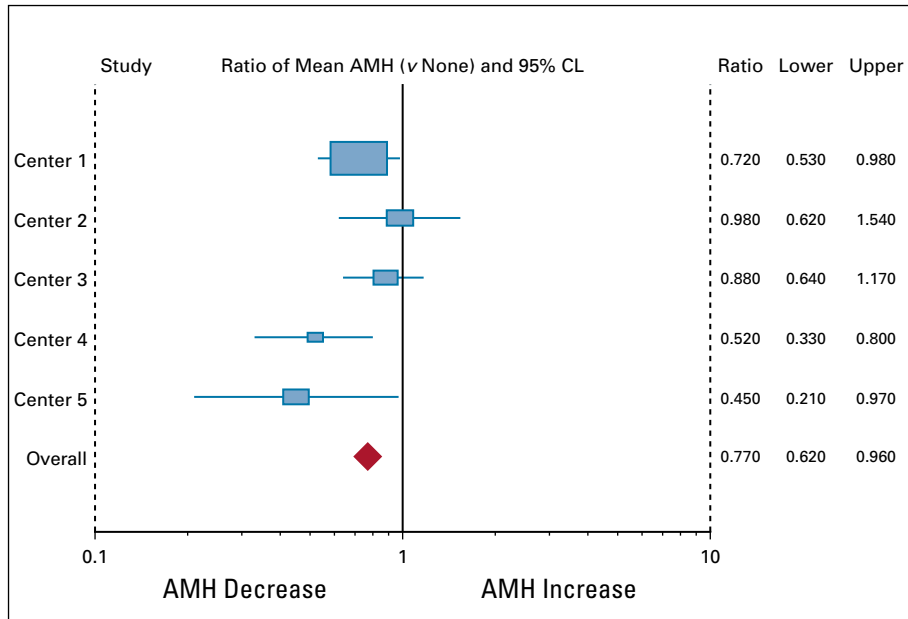


FIG 2. AMH values by BRCA. Forest plot analysis of individual results from five participating centers. One is null value of 0 difference or decrease. Individual centers were minimally adjusted, whereas overall data were adjusted for center, age, smoking, OCP, and BMI. AMH, anti-Müllerian hormone; BMI, body mass index; OCP, oral contraceptive pills.

3.59 ng/mL in women without *gBRCA* (SD = 3.2, median of 2.8, and geometric mean of 2.31). After adjusting for center, age, smoking status, BMI, and OCP use, affected women with *gBRCA* had significantly lower AMH levels compared with women without *gBRCA* (25% lower, 95% CI, 9 to 38; *P* = .003). Furthermore, after adjusting for center, age, smoking, and OCP use, AMH levels of women with *gBRCA1* were lower compared with the controls (32% lower, 95% CI, 14% to 46% lower; *P* = .001). The serum AMH levels of affected women with *gBRCA2* showed no significant difference in comparison with controls (14% lower, 95% CI, 34% lower to 12% higher; *P* = .25).

Secondary or Sensitivity Analysis With RE Versus FE

When we fitted a random effects (RE) model as a secondary or sensitivity analysis, our analysis also showed robust results. For example, when we estimated % decrease in mean AMH between *gBRCA1/2* and none, adjusting

center, and age only, our original analysis yielded 26 (95% CI, 9 to 39; *P* = .004), whereas a newly fitted RE model yielded 27 (15 to 37; *P* ≤ .0001). As another extreme case with only affected women, adjusting for center/age/smoking and OCP use, the estimated % decrease was 25 (9 to 38; *P* = .003) versus 25 (10 to 38; *P* = .002) for these two models, respectively. This sensitivity analysis shows that the FE model that we used for the primary analysis for our IPD data was slightly more conservative than the RE model.

DISCUSSION

We performed an IPD analysis from five centers to investigate the relationship between *gBRCA* and AMH levels. After adjusting for potential confounders, we found that women with *gBRCA*, specifically those affected and carrying *gBRCA1*, have lower serum AMH levels compared with women without *gBRCA*. To our knowledge, this is the

TABLE 2. AMH Values by Overall *gBRCA* Status (*gBRCA1* and *gBRCA2* Combined)

Adjustment	% Decrease in Mean AMH (95% CI) <i>gBRCA1/2</i> v None	<i>P</i>
Center and age (N = 824)	26 (9 to 39)	.004
Center, age, smoking, and OCP (N = 824 ^a)	26 (9 to 39)	.004
Center, age, smoking, OCP, and BMI (N = 720 ^a)	23 (4 to 38)	.02
Center, age, smoking, and OCP; only affected women (excluding center 1) (N = 681)	25 (9 to 38)	.003

NOTE. Pooled analysis with stepwise adjustment for center, age, smoking status, OCP use, and BMI.

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; OCP, oral contraceptive pills.

^aWe included missing data as a category for smoking and OCP but did not impute missing BMI.

TABLE 3. AMH Values by *gBRCA1* v *gBRCA2*

Adjustment	% Decrease in Mean AMH (95% CI), Adjusting Age		P
	<i>gBRCA1</i> v Negative	<i>gBRCA2</i> v Negative	
Center and age	34 (17 to 49)		.0004
	10 (32 to -19 ^a)		.47
Center, age, smoking, and OCP	35 (18 to 49)		.0004
	9 (31 to -21)		.52
Center, age, smoking, OCP, and BMI	33 (12 to 49)		.004
	7 (31 to -26)		.64
Center, age, smoking, and OCP; only affected women (excluding center 1)	32 (14 to 46)		.001
	14 (34 to -12)		.25

NOTE. Pooled analysis with stepwise adjustment for center, age, smoking status, OCP use, and BMI.

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; OCP, oral contraceptive pills.

^aNegative number means increase.

first multicenter analysis and the largest study investigating the relationship between *gBRCA* and AMH levels in women with or at risk for breast cancer.

Oktay et al³ first reported low response to ovarian stimulation and subsequently lower serum AMH levels in women with breast cancer.⁵ This was followed by several studies supporting the finding of lower serum AMH in both affected and unaffected women with *gBRCA*,^{5,11,13,20} but others were unable to detect similar differences.^{14,18,19} We have recently reviewed the published evidence on the impact of *gBRCA* on ovarian aging and discussed the limitations and possible reasons for discrepancies among the studies.⁶ This individual patient level meta-analysis of published and updated data was performed to overcome the shortcomings of distinct studies. The current study confirmed the findings from most studies that particularly the presence of a *gBRCA1* negatively affects the ovarian reserve of young women affected with or at risk for breast cancer.

Laboratory studies in human ovarian tissue have determined the potential mechanism of diminished oocyte reserve in women with *gBRCA*. *BRCA1/2* are the members of the ataxia-telangiectasia mutated (ATM)-mediated DNA DSB repair pathway. Inadequate repair of DNA DSBs results in severe mutagenesis leading to carcinogenesis and tissue aging.^{26,27} The ATM-mediated DNA DSB repair pathway is charged with repair of this most lethal form of DNA damage, which is estimated to occur nearly a million times every day.²⁶ The basic research from Dr Oktay's laboratory showed that *gBRCA1* but not the *gBRCA2* mutant mice have fewer primordial follicles that accumulate more DNA DSBs in their oocytes with age compared with the wild type mice. These mice also ovulate fewer oocytes and have lower litter size than the controls.⁵

The same team has also shown that the ovaries of women with *gBRCA* carry fewer primordial follicles, which are lost in an accelerated manner and accumulate more DNA DSBs with age compared with ovaries from controls.¹² Oktay's

laboratory also showed that gonadotoxic chemotherapy induces primordial follicle death and ovarian reserve loss by inducing DNA DSBs and apoptosis of oocytes and some oocytes may be able to repair themselves by activating the ATM pathway.²⁸ In addition, recent longitudinal and laboratory data suggest that women with *gBRCA* may lose larger ovarian reserve after chemotherapy because of oocyte DNA repair deficiency.^{22,29,30} This may be a double whammy for affected women with *gBRCA* as their already lower ovarian reserve status is compounded by larger chemotherapy-induced loss, rendering them highly liable for infertility. However, further studies will be needed to confirm that women with *gBRCA* lose clinically significantly larger ovarian reserve after chemotherapy, compared with those without mutations.

In fact, *BRCA1* and other ATM pathway genes and the age-induced decline in their function appear to be central in ovarian aging.^{5,6} *BRCA1* has a more complex involvement in the ATM-mediated DNA DSB repair pathway than *BRCA2*. Although *BRCA1* plays a role in damage sensing, homologous recombination repair, and checkpoint regulation (such as through CHEK2), the role of *BRCA2* is limited to homologous recombination only. Moreover, the age-related decline in the *BRCA1* function has been shown to occur earlier than the *BRCA2* function in human oocytes.⁵ Although that decline appears to become prominent in the third decade of life in women with *gBRCA1*, the same may not happen until the fourth decade in the case of *gBRCA2*.⁵ Because women with *gBRCA* have one dysfunctional allele, age-induced decline in the function of the intact allele results in an acquired homozygosity with age.³⁰ This then results in the accelerated accumulation of DNA DSBs in human oocytes, which triggers apoptotic death mechanisms of cell senescence, resulting in the accelerated reduction of ovarian reserve.^{5,6,22} Because the function of *BRCA1* declines earlier in life than that of *BRCA2*, this may

explain why ovarian reserve loss is more prominent in women with *gBRCA1* compared with *gBRCA2*.

Considering the possibility that the affected women may have more severely accelerated ovarian aging, we analyzed our data with and without the inclusion of unaffected women, but this analysis did not alter our results. In our IPD analysis, only one center (Cedars Sinai Medical Center, Los Angeles, CA) studied unaffected women and found lower serum AMH level in those with *gBRCA1*. In this meta-analysis, we included all published studies in affected women, whereas the nonparticipating studies, except for one (Gunnala et al¹⁸ studied both affected and unaffected women), were performed among the unaffected (Data Supplement). In total, there have been six studies that assessed the relationship between *gBRCA1/2* and AMH levels only in unaffected women. Although two studies were negative,^{14,19} four showed that there were lower AMH levels in women with *gBRCA1/2*,³¹ with only *gBRCA1*^{13,32} or only *gBRCA2*.¹⁵ Therefore, although the preponderance of evidence also suggests lower serum AMH level in unaffected women compared with controls, further research is needed to determine the magnitude of serum AMH differences between affected and unaffected women and those with *gBRCA1* versus *gBRCA2*. Therefore, our findings are on firmer ground with affected women with *gBRCA*.

There is other evidence supporting lower ovarian reserve in women with *gBRCA*. Several studies showed earlier menopausal age, particularly for those with *gBRCA1*.^{16,33} A large meta-analysis of genome-wide association analysis identified polymorphism in the *BRCA1* as one of the key determinants of age at natural menopause.³⁴

It is also possible that the differences we have reported here are underestimations as those most severely affected might have already had early risk reducing salpingo-oophorectomy and/or developed early breast or ovarian cancer or menopause and lose their reproductive function iatrogenically.^{35,36} These patients would then not be accounted in studies analyzing serum AMH.

Although there is no uniform normal range for AMH, in general, the mean value of 2.0 ng/mL in *gBRCA* in our IPD meta-analysis is well below the lower range of age-matched normal (2.9 ng/mL).³⁷ Within that range, an average difference of 1.32 ng/mL is highly significant as it is 35% lower than the controls, which could translate into a shortening of reproductive life period by 10 years.³⁸

Despite our repeated efforts, we could not obtain raw data from seven of 12 studies we identified, all involving unaffected woman. Because the data from the nonparticipating studies greatly varied in data format, availability, and/or quality, it was not possible to perform any reasonable meta-analysis or preliminary data processing or standardization as a sensitivity or secondary analysis. However, the five studies that were included represent > 80% of all published data on affected women. For this reason, our analysis is robust for the relationship between *gBRCA* and ovarian reserve in women who developed breast cancer. However, the nonparticipation of seven studies that nearly exclusively studied unaffected women does not allow us to reach a firm conclusion on the association of diminished ovarian reserve with *gBRCA* in unaffected carriers.

In conclusion, by IPD analysis from five centers, we showed that women with *gBRCA* have lower AMH levels compared with those without, and this appeared to be restricted to those with *gBRCA1*. Therefore, based on this IPD analysis and the supporting basic science and translational data,^{5,6,39} we recommend that especially the affected women with *gBRCA1* should proactively receive reproductive and fertility preservation counseling if they are postponing childbearing to the third decade and beyond. This conclusion is firmer for affected women as our IPD meta-analysis predominantly studied those with breast cancer, but further original and meta-analytic studies are needed to determine if there is a difference between the ovarian reserve of affected and unaffected women with *gBRCA* and to understand the magnitude of ovarian reserve differences between women with *gBRCA1* and *gBRCA2*.

AFFILIATIONS

¹Department of Obstetrics and Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT

²Department of Obstetrics and Gynecology, Health and Technology University School of Medicine, Istanbul, Turkey

³Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy

⁴Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy

⁵Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

⁶Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA

⁷Department of Medical Oncology, Henri Becquerel Centre, Rouen, France

⁸UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA

⁹Fertility Clinic, Research Laboratory on Human Reproduction, CUB-Erasme, and Université Libre de Bruxelles (ULB), Brussels, Belgium

¹⁰Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, CA

¹¹Innovation Institute for Fertility Preservation, New York, NY

CORRESPONDING AUTHOR

Kutluk Oktay, MD, PhD, Yale School of Medicine, 333 Cedar St, New Haven, CT 06510; e-mail: kutluk.oktay@fertilitypreservation.org.

SUPPORT

Supported by R01 HD053112 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Cancer Institute. H.B. was partly supported by the National Institutes of Health through grant UL1 TR001860.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.20.02880>.

AUTHOR CONTRIBUTIONS

Conception and design: Volkan Turan, Kutluk Oktay

Administrative support: Kutluk Oktay

Provision of study materials or patients: Matteo Lambertini, Erica Wang, Florian Clatot, Beth Y. Karlan, Isabelle Demeestere, Kutluk Oktay

Collection and assembly of data: Volkan Turan, Matteo Lambertini, Dong-Yun Lee, Erica Wang, Florian Clatot, Beth Y. Karlan, Isabelle Demeestere, Kutluk Oktay

Data analysis and interpretation: Volkan Turan, Heejung Bang, Kutluk Oktay

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

- Venkitaraman AR: Beyond cancer genomics: After the end of the beginning. *Curr Opin Genet Dev* 22:1-2, 2012
- Rebbeck TR, Mitra N, Wan F, et al: The CIMBA Consortium Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA* 313:1347-1361, 2015
- Oktay K, Kim JY, Barad D, et al: Association of BRCA1 mutations with occult primary ovarian insufficiency: A possible explanation for the link between infertility and breast/ovarian cancer risks. *J Clin Oncol* 28:240-244, 2010
- Turan V, Bedoschi G, Emirdar V, et al: Ovarian stimulation in patients with cancer: Impact of letrozole and BRCA mutations on fertility preservation cycle outcomes. *Reprod Sci* 25:26-32, 2018
- Titus S, Li F, Stobezki R, et al: Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. *Sci Transl Med* 5:172ra21, 2013
- Turan V, Oktay K: BRCA-related ATM-mediated DNA double-strand break repair and ovarian aging. *Hum Reprod Update* 26:43-57, 2020
- Lambertini M, Goldrat O, Toss A, et al: Fertility and pregnancy issues in BRCA-mutated breast cancer patients. *Cancer Treat Rev* 59:61-70, 2017
- Tal R, Seifer DB: Ovarian reserve testing: A user's guide. *Am J Obstet Gynecol* 217:129-140, 2017
- Ulrich ND, Marsh EE: Ovarian reserve testing: A review of the options, their applications, and their limitations. *Clin Obstet Gynecol* 62:228-237, 2019
- Lambertini M, Goldrat O, Ferreira AR, et al: Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. *Ann Oncol* 29:237-243, 2018
- Wang ET, Pisarska MD, Bresee C, et al: BRCA1 germline mutations may be associated with reduced ovarian reserve. *Fertil Steril* 102:1723-1728, 2014
- Lin W, Titus S, Moy F, et al: Ovarian aging in women with BRCA germline mutations. *J Clin Endocrinol Metab* 102:3839-3847, 2017
- Giordano S, Garrett-Mayer E, Mittal N, et al: Association of BRCA1 mutations with impaired ovarian reserve: Connection between infertility and breast/ovarian cancer risk. *J Adolesc Young Adult Oncol* 5:337-343, 2016
- van Tilborg TC, Broekmans FJ, Pijpe A, et al: Do BRCA1/2 mutation carriers have an earlier onset of natural menopause? *Menopause* 23:903-910, 2016
- Johnson L, Sammel MD, Domchek S, et al: Anti-Müllerian hormone levels are lower in BRCA2 mutation carriers. *Fertil Steril* 107:1256-1265.e6, 2017
- Rzepka-Gorska I, Tarnowski B, Chudecka-Głaz A, et al: Premature menopause in patients with BRCA1 gene mutation. *Breast Cancer Res Treat* 100:59-63, 2006
- Oktay K, Turan V, Titus S, et al: BRCA mutations, DNA repair deficiency and ovarian aging. *Biol Reprod* 93:67, 2015
- Gunnala V, Fields J, Irani M, et al: BRCA carriers have similar reproductive potential at baseline to noncarriers: Comparisons in cancer and cancer-free cohorts undergoing fertility preservation. *Fertil Steril* 111:363-371, 2019
- Michaelson-Cohen R, Mor P, Srebnik N, et al: BRCA mutation carriers do not have compromised ovarian reserve. *Int J Gynecol Cancer* 24:233-237, 2014
- Son KA, Lee DY, Choi D: Association of BRCA mutations and anti-Müllerian hormone level in young breast cancer patients. *Front Endocrinol (Lausanne)* 10:235, 2019
- Lambertini M, Olympios N, Lequesne J, et al: Impact of taxanes, endocrine therapy, and deleterious germline BRCA mutations on anti-Müllerian hormone levels in early breast cancer patients treated with anthracycline- and cyclophosphamide-based chemotherapy. *Front Oncol* 9:575, 2019
- Oktay K, Bedoschi G, Goldfarb S, et al: Increased chemotherapy-induced ovarian reserve loss in women with germline BRCA mutations due to oocyte deoxyribonucleic acid double strand break repair deficiency. *Fertil Steril* 113:1251-1260.e1, 2020
- Kahan BC: Accounting for centre-effects in multicentre trials with a binary outcome—when, why, and how? *BMC Med Res Methodol* 14:20, 2014
- Fitzmaurice GM, Laird NM, Ware JH: *Applied Longitudinal Analysis*, Volume 7 (ed 2). John Wiley & Sons, section 9.7, 2011
- Riley RD, Lambert PC, Abo-Zaid G: Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ* 340:c221, 2010
- Roos WP, Kaina B: DNA damage-induced cell death: From specific DNA lesions to the DNA damage response and apoptosis. *Cancer Lett* 332:237-248, 2013
- Cohen IS, Bar C, Paz-Elizur T, et al: DNA lesion identity drives choice of damage tolerance pathway in murine cell chromosomes. *Nucleic Acids Res* 43:1637-1645, 2015
- Soleimani R, Heytens E, Darzynkiewicz Z, et al: Mechanisms of chemotherapy-induced human ovarian aging: Double strand DNA breaks and microvascular compromise. *Aging (Albany NY)* 3:782-793, 2011
- Oktay K, Moy F, Titus S, et al: Age-related decline in DNA repair function explains diminished ovarian reserve, earlier menopause, and possible oocyte vulnerability to chemotherapy in women with BRCA mutations. *J Clin Oncol* 32:1093-1094, 2014
- Goldfarb SB, Turan V, Bedoschi G, et al: Impact of adjuvant chemotherapy or tamoxifen-alone on the ovarian reserve of young women with breast cancer. *Breast Cancer Res Treat* 185:165-173, 2021
- Ben-Aharon I, Levi M, Margel D, et al: Premature ovarian aging in BRCA carriers: A prototype of systemic precocious aging? *Oncotarget* 9:15931-15941, 2018
- Phillips KA, Collins IM, Milne RL, et al: Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations. *Hum Reprod* 31:1126-1132, 2016

33. Finch A, Valentini A, Greenblatt E, et al: Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. *Fertil Steril* 99:1724-1728, 2013
34. Day FR, Ruth KS, Thompson DJ, et al: Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. *Nat Genet* 47:1294-1303, 2015
35. Lin WT, Beattie M, Chen LM, et al: Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. *Cancer* 119:1652-1659, 2013
36. Santoro N: BRCA mutations and fertility: Do not push the envelope! *Fertil Steril* 99:1560, 2013
37. Almog B, Shehata F, Suissa S, et al: Age-related normograms of serum antimullerian hormone levels in a population of infertile women: A multicenter study. *Fertil Steril* 95:2359-2363, 2011
38. Tehrani FR, Solaymani-Dodaran M, Tohidi M, et al: Modeling age at menopause using serum concentration of anti-mullerian hormone. *J Clin Endocrinol Metab* 98:729-735, 2013
39. Govindaraj V, Krishnagiri H, Chakraborty P, et al: Age-related changes in gene expression patterns of immature and aged rat primordial follicles. *Syst Biol Reprod Med* 63:37-48, 2017



ASCO® Meetings

ASCO offers premier scientific events for oncology professionals, patient advocates, industry representatives, and major media outlets worldwide.

View upcoming meetings and symposia at meetings.asco.org

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association of Germline *BRCA* Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Matteo Lambertini

Consulting or Advisory Role: Roche, Novartis, Lilly, AstraZeneca

Speakers' Bureau: Theramex, Takeda, Roche, Lilly, Novartis, Pfizer, Sandoz

Erica Wang

Consulting or Advisory Role: OncoPep

Research Funding: Merck

Florian Clatot

Honoraria: Merck Serono, Bristol-Myers Squibb, AstraZeneca

Consulting or Advisory Role: Lilly, Bristol-Myers Squibb, Roche, Merck Serono

Research Funding: AstraZeneca, Roche Diagnostics

Travel, Accommodations, Expenses: Merck Serono, Roche, Bristol-Myers Squibb

Beth Y. Karlan

Consulting or Advisory Role: Roche Pharma AG, Merck, Mercy BioAnalytics

Research Funding: VBL Therapeutics, AstraZeneca

Patents, Royalties, Other Intellectual Property: US and EU patent on gene signature

Other Relationship: Elsevier

Isabelle Demeestere

Consulting or Advisory Role: Roche

Research Funding: Roche Diagnostics

Travel, Accommodations, Expenses: Ferring

No other potential conflicts of interest were reported.