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Reduced reproductive potential in young healthy women with hereditary breast and/or ovarian cancer syndrome

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Abstract

Background Young, healthy women carrying a pathogenic or likely pathogenic variant (P/LPV) in genes configuring the hereditary breast and/or ovarian cancer (HBOC) syndrome face several non-oncological issues. Among these, the implications on fertility are not yet entirely understood.

Methods Aiming to explore the ovarian reserve in young, healthy women with HBOC syndrome, we conducted a monocentric, prospective, observational cohort trial between January 2020 and September 2023. Eighty-seven healthy women aged less than 42 years with a P/LPV in HBOC predisposition genes were enrolled: 32 *BRCA1* P/LPV carriers, 47 *BRCA2* P/LPV carriers, and 8 carriers of P/LPV in other genes (*TP53, RAD50, CHECK2, RAD51D, PALB2, ATM*). AMH levels and antral follicular count (AFC) were evaluated as fertility biomarkers.

Results No significant differences in demographic characteristics or mean levels of AMH or in AFC are observed between *BRCA1* and *BRCA2* P/LPV carriers. The distribution of AMH values is significantly lower compared to the general population ($p = 0.019$). The significant decrease in AMH levels is mostly ascribable to *BRCA1* P/LPV carriers ($p = 0.03$). Both in the overall population and in *BRCA1/2* P/LPV carriers, AFC decreases faster compared to those reported in the nomogram.

Conclusions A consistent trend for reduced reproductive potential in young, healthy women with HBOC syndrome is observed, particularly in *BRCA1* P/LPV carriers. These findings need to be confirmed by larger studies including also women carrying P/LPV in other HBOC syndrome-related genes.

Plain language summary

Some young, healthy women have an increased chance of developing breast and/or ovarian cancer because they have inherited mutated genes from their parents. This is known as hereditary breast and/or ovarian cancer (HBOC) syndrome. We investigated whether these women also had issues with fertility. We measured two indicators of ovarian reserve. The ovarian reserve is the number of healthy eggs that a woman has in her ovaries. We found a trend for reduced reproductive potential in young, healthy women with HBOC syndrome. If these findings are confirmed by larger studies, fertility counseling could be helpful for this specific population of women.

Harboring a germline pathogenic or likely pathogenic variant (P/LPV) in *BRCA1/2* is associated with an increased lifetime risk of breast and ovarian cancer. More specifically, the cumulative risk of breast and ovarian cancer by 80 years of age is 72% and 44% for *BRCA1* P/LPV carriers and 69% and 17% for *BRCA2* P/LPV carriers, respectively. In *BRCA1/2* P/LPV carriers, breast cancer often occurs during reproductive age, while ovarian cancer is rare before 40–45 years of age[1]. Besides these well-defined high penetrance genes, other genes can increase the susceptibility to breast and/or ovarian cancers. In detail, the most prevalent high and moderate penetrant genes are *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *CDH1*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*. Low penetrant genes are *FANCC*, *MRE11A*, *NBN*, *RECQL4*, *RAD50*, *RINT1*, *SLX4*, *SMARCA4*, and *XRCC2*[2]. Germline P/LPVs in one of these genes configure hereditary breast and/or ovarian cancer (HBOC) syndrome. The identification of HBOC syndrome plays a crucial role in the management of hereditary cancer prevention, diagnosis and treatment[3–20].

Importantly, besides concerns for increased cancer risk, young women carrying a germline P/LPV in HBOC predisposition genes face several non-

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oncological issues that affect the quality of their reproductive life. First of all, the premature menopause induced by risk-reducing salpingo-oophorectomy may cause hot flashes, cognitive changes, vaginal dryness, sleep disturbances, and increased risk for osteoporosis and cardiovascular disorders[21–23]. Moreover, the risk-reducing bilateral mastectomy in BRCA-carriers and the breast surgery in BRCA-cancer patients may affect body image perception and sexual functioning[24,25]. Finally, previous researches indicated that female carriers of a *BRCA* P/LPV may display lower ovarian reserve, tendency to experience premature menopause, increased ovarian aging, decreased anti mullerian hormone (AMH) level, and lower ovarian response to ovarian stimulation than non-carriers[26–32]. Nevertheless, the implications of germline P/LPVs on women's fertility are not yet entirely understood.

The anti-mullerian hormone (AMH) is a dimeric glycoprotein solely produced from granulosa cells of preantral (primary and secondary) and small antral follicles[33]. The number of small antral follicles directly correlates with the primordial follicle pool. As the amount of antral follicles diminishes with age, AMH serum levels decrease to the point of becoming almost undetectable at menopause[34,35]. Moreover, AMH levels reflect the ovarian reserve, thus predicting menopause age[36,37]. On the other hand, the quantity of primordial follicles corresponds with the number of antral follicles at every age. With ageing, the primordial follicle pool parallelly decreases with the amount of antral follicles sensitive to FSH[38]. The correlation between antral follicle count (AFC) and the onset of menopausal transition has been investigated in two studies, thus demonstrating the close relationship with the quantitative aspect of ovarian reserve[39–41].

The aim of this study is to explore ovarian reserve in young, healthy women carrying germline P/LPVs in HBOC predisposition genes, evaluating AMH and AFC as fertility biomarkers. We observe a consistent trend for reduced reproductive potential in young, healthy women with HBOC syndrome, particularly in BRCA1 pathogenic/likely-pathogenic variant carriers.

Methods

Study participants

This is a monocentric, prospective, observational, cohort trial conducted at the Modena Family Cancer Clinic (MFCC), Italy, between January 2020 and September 2023. In the Emilia-Romagna region (Italy), women with a family history of breast and/or ovarian cancer are currently invited to a first-level evaluation at one of the 13 Spoke Centers. On the basis of their lifetime breast cancer risk assessed by risk prediction models such as the Gail and Tyrer-Cuzick models[42], they are offered a chance to join a personalized surveillance program. After the first evaluation, some of them move on to a second-level evaluation at a HUB Center to assess the need for a genetic testing in the family. The MFCC is one of the four HUB Centers in Emilia-Romagna for the identification of families at increased familial or hereditary cancer risk. To date, more than 900 women who carry a genetic P/LPV predisposing to breast and/or ovarian cancer have attended the MFCC for their screening programs.

We enrolled healthy women carrying a germline P/LPV in one of the breast and/or ovarian cancer predisposition genes, aged less than 42 years. Women with previous ovarian surgery, history of cystectomy or detection of current ovarian cyst at the time of ultrasonography, personal history of cancer, current or past use of hormonal contraceptive methods within the last 6 months, and pregnancy or breastfeeding were excluded from the study.

Procedure

At study entry, participants filled out an epidemiologic questionnaire assessing body mass index (BMI), menstrual history, parity, use of hormonal contraceptive methods, fertility treatment, and smoking status. After informed consent was provided, blood samples were obtained to determine AMH level, and transvaginal ultrasound (TV-US) was performed by an experienced operator (G.S.) to evaluate AFC. Blood samples were collected and TV-US was performed on the day of patient recruitment, regardless of the last menstrual cycle. The blood was centrifuged at 2000 *g* for 10 min, and the serum was stored in polypropylene tubes at −80 °C. Serum AMH was measured through the new automated Access AMH assay (Beckman Coulter). AMH values were then compared with the Roche Diagnostics (Elecsys) nomogram. This nomogram was based on a control population of 887 women not taking contraceptives from 20 to 50 years of age (Roche study No. RD001727). This population included 150 women aged between 20–24 years, 150 aged 25–29 years, 138 aged 30–34 years, 138 aged 35–39 years, 142 aged 40–44 years and, 169 aged 45–50 years. The participants' AFC values were compared with those of one of the most recent nomogram for AFC in the general population. This nomogram was based on the same control population used in the AMH nomogram by Bozdag: 381 women aged between 20–50 years with regular menstrual bleeding and without hirsutism, menstrual irregularity, diagnosis of current/history of endometrioma, and hormonal drug use within the last 6 months[43].

Institutional ethical approval by the Area Vasta Emilia Nord Ethics Committee was granted for the study protocol according to the Declaration of Helsinki principles. Informed consent was obtained from all patients recruited.

Statistics

The primary objective of the study was to evaluate ovarian reserve for healthy carriers of germline P/LPVs in genes predisposing to HBOC syndrome, defined by AMH levels in ng/mL and AFC. Descriptive statistics were produced for the characteristics of the subjects under analysis. Numerical variables were reported as mean and standard deviation (SD), whereas categorical variables were expressed through absolute frequencies and percentages. The correlation between outcome measures and patient characteristics was investigated through univariable and multivariable linear regression models. Age, BMI, and smoking status were included in the models as covariates, in order to adjust the estimation of the relationship between genetic P/LPVs and ovarian reserve.

The association between AMH and AFC was also investigated. Univariable linear regression models were fitted to study this association and assess how it is affected by *BRCA*1 and *BRCA2* P/LPVs. Results were reported in terms of mean difference (MD), with 95% confidence interval (95%CI) and *p*-values. AMH was measured through the Beckman Coulter Access assay, while the distribution of values was compared with that of AMH in the general population, obtained by Roche Elecsys assay using the conversion factor from Access to Elecsys (Elecsys = −0.06 þ 0.88 x Access)[44]. The analysis of AMH and AFC against the available nomogram curves was performed by comparing the observed frequencies of subjects in each percentile with their expected proportions, stratifying by age. Pearson's test was used to assess the difference between these proportions. All results were considered significant when associated with a p-value < 0.05. The analyses were carried out through the statistical software R version 4.2.2 (The R Foundation for Statistical Computing, 2022).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Study population

Eighty-seven women were enrolled in the study. Thirty-two women carried a *BRCA1* P/LPV, and 47 carried a *BRCA2* P/LPV, whereas 8 women had a P/LPV in genes other than *BRCA1/2* (two in *ATM*, two in *PALB2*, one in *CHECK2*, one in *RAD50*, one in *RAD51D*, and one in *TP53*).

No significant differences were observed between the epidemiologic characteristics of *BRCA1* and *BRCA2* P/LPV carriers (Table 1). The mean age at time of enrollment of the whole HBOC cohort was 32.3 years (32.3 in *BRCA1* and 32.2 in *BRCA2*), the mean BMI was 23.5 (24 in *BRCA1* and 22.9 in *BRCA2*), and the mean age at menarche was 12.3 years (11.9 in *BRCA1* and 12.4 in *BRCA2*). Overall, seventy-eight women (89.7%) reported regular menstrual cycles and 49 women (56.3%) reported previous use of hormonal

Table 1 | Characteristics of the overall population (HBOC), *BRCA1* P/LPV carriers and *BRCA2* P/LPV carriers

	HBOC 87 patients			BRCA1 P/LPV carriers 32 patients			BRCA2 P/LPV carriers 47 patients			BRCA1 Vs BRCA2
	Mean	SD	Miss.	Mean	SD	Miss.	Mean	SD	Miss.	*p*-value
Age	32.31	5.73	0	32.31	5.33	0	32.17	6.32	0	0.914
Hormonal contraceptive use (years)	5.76	5.72	40 (46%)	5.25	5.22	12 (38%)	5.67	6.50	25 (53%)	0.819
Menarche (years)	12.26	1.48	0	11.95	1.40	0	12.40	1.54	0	0.182
Length of menstrual cycle (days)	28.18	2.35	9 (10%)	28.10	2.11	3 (9%)	28.14	2.66	5 (11%)	0.945
BMI	23.52	4.39	1 (1%)	23.98	3.88	0	22.94	4.81	1 (2%)	0.292
AMH (ng/ml)	2.62	1.86	1 (1%)	2.92	2.06	0	2.43	1.75	1 (2%)	0.278
AFC (*n*)	16.20	9.97	2 (2%)	16.06	9.02	0	15.98	10.96	2 (4%)	0.971
	N	**Perc.**	**Miss.**	***N***	**Perc.**	**Miss.**	***N***	**Perc.**	**Miss.**	
Previous pregnancies (*n*)			0			0			0	0.946
0	44	50.57		16	50.00		25	53.19		
1	13	14.94		5	15.63		7	14.89		
2	21	24.14		9	28.13		10	21.28		
3	5	5.75		1	3.13		3	6.38		
4	4	4.60		1	3.13		2	4.26		
Previous deliveries (n)			0			0			0	0.936
0	48	55.17		18	56.25		26	55.32		
1	16	18.39		6	18.75		9	19.15		
2	19	21.84		7	21.88		9	19.15		
3	3	3,45		1	3.13		2	4.26		
4	1	1.15		0	0.00		1	2.13		
Previous termination of pregnancy (n)			0			0			0	0.883
0	70	80.46		26	81.25		40	85.11		
1	12	13.79		5	15.63		5	10.64		
2	5	5.75		1	3.13		2	4.26		
Current smoking			0			0			0	0.518
No	71	81.61		24	75.00		40	85.11		
Yes	16	18.39		8	25.00		7	14.89		
Family history of premature menopause			0			0			0	0,178
No	80	91.95		29	90.63		43	91.49		
Yes	7	8.05		3	9.38		4	8.51		
Prophylactic surgery			0			0			0	1,000
None	79	90.80		28	87.50		43	91.49		
Mastectomy	6	6.90		3	9.38		3	6.38		
Salpingectomy	1	1.15		0	0.00		1	2.13		
Mastectomy and salpingectomy	1	1,.15		1	3.13		0	0.00		

AFC antral follicle count, *AMH* anti-mullerian hormone, *BMI* body mass index, *HBOC* hereditary breast and/or ovarian cancer, *Miss* missing, *Per* percentage, *P/LPV* pathogenic/likely pathogenic variants. *SD* standard deviation.

contraceptive methods with a mean duration of previous exposure of 5.8 years (5.2 in *BRCA1* and 5.7 in *BRCA2*). However, none of the patients enrolled were under treatment at the time of recruitment and study. Forty-eight women (55.2%) were nulliparous, and forty-four (50.5%) never had a pregnancy. Seventeen women (19.5%) reported at least one spontaneous termination of pregnancy during the first trimester.

Sixteen women (18.4%) were current smokers (8 *BRCA1* and 7 *BRCA2*), and 6 (6.7%) were past smokers. Seven women (8%) reported a positive family history of premature menopause (before the age of 40). Eight women underwent risk-reducing surgery: 6 had risk-reducing mastectomy, 1 had risk-reducing salpingectomy, and 1 had both risk-reducing mastectomy and salpingectomy (3 risk-reducing mastectomy in *BRCA1*, 3 risk-reducing mastectomy in *BRCA2*, 1 risk-reducing salpingectomy in *BRCA2*, and 1 both mastectomy and salpingectomy in *BRCA1*).

For the evaluation of AMH levels and AFC compared to the nomogram, patients were therefore divided into three groups according to age at enrollment. 29 women (33.3%) belonged to the 20–29 years group, 23 (26.4%) to the 30–34 years group and, 35 (40.2%) to the ≥35 years group.

Serum AMH Levels

Eighty-six patients (32 *BRCA1*, 46 *BRCA2*, 8 other genes) had an available AMH level for the analysis. The overall mean AMH level was 2.6 ng/mL (SD 1.85, median 2.32), with 2.92 ng/mL (SD 2.06, median 2.06) in *BRCA1* P/LPV carriers and 2.43 ng/mL in *BRCA2* P/LPV carriers (SD 1.73, median of

Table 2 | Distribution of AMH values in the HBOC population, *BRCA1* P/LPV carriers and BRCA2 P/LPV carriers compared with the expected nomogram for the general population

	Percentile Distribution in Study Population (HBOC)					Nomogram				
Age	**0–5**	**5–50**	**50–95**	**95–100**	**Total**	**0–5**	**5–50**	**50–95**	**95–100**	***p-value***
20–29	5 (18%)	11 (39%)	12 (43%)	0 (0%)	28 (100%)	5%	45%	45%	5%	0.012
30–34	0 (0%)	13 (57%)	9 (39%)	1 (4%)	23 (100%)	5%	45%	45%	5%	0.567
≥35	5 (14%)	11 (31%)	19 (54%)	0 (0%)	35 (100%)	5%	45%	45%	5%	0.020
Total	10 (12%)	35 (41%)	40 (47%)	1 (1%)	86 (100%)	5%	45%	45%	5%	0.019
	Percentile Distribution in BRCA1 P/LPV carriers					**Nomogram**				
20–29	3 (27%)	4 (36%)	4 (36%)	0 (0%)	11 (100%)	5%	45%	45%	5%	0.008
30–34	0 (0%)	4 (44%)	4 (44%)	1 (11%)	9 (100%)	5%	45%	45%	5%	0.771
≥35	2 (17%)	2 (17%)	8 (67%)	0 (0%)	18 (100%)	5%	45%	45%	5%	0.064
Total	5 (16%)	10 (31%)	16 (50%)	1 (3%)	32 (100%)	5%	45%	45%	5%	0.030
	Percentile Distribution in BRCA2 P/LPV carriers					**Nomogram**				
20–29	2 (13%)	6 (38%)	8 (50%)	0 (0%)	16 (100%)	5%	45%	45%	5%	0.409
30–34	0 (0%)	7 (70%)	3 (30%)	0 (0%)	10 (100%)	5%	45%	45%	5%	0.409
≥35	2 (10%)	8 (40%)	10 (50%)	0 (0%)	20 (100%)	5%	45%	45%	5%	0.528
Total	4 (9%)	21 (46%)	21 (46%)	0 (0%)	46 (100%)	5%	45%	45%	5%	0.312

HBOC hereditary breast and/or ovarian cancer, *P/LPV* pathogenic/likely pathogenic variants.

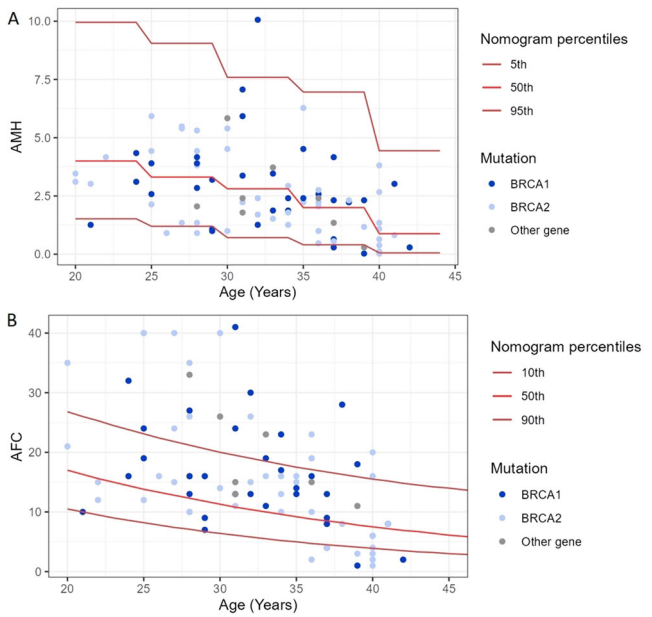

Fig. 1 | Fertility biomarkers in the overall population. A AMH values (32 *BRCA1*, 46 *BRCA2*, 8 other genes) and (**B**) AFC (32 *BRCA1*, 45 *BRCA2*, 8 other genes) observed vs nomogram curves in the overall population. AMH anti mullerian hormone. AFC antral follicular count.

2.18). For AMH mean levels, no significant difference was observed between *BRCA1* and *BRCA2* P/LPV carriers ($p = 0.263$). Considering overall the HBOC cohort, the distribution of AMH values in our study population was significantly lower than that reported for the general population ($p = 0.019$) (Table 2, Fig. 1A). In the 20–29 and ≥35 years of age group, AMH levels were significantly lower compared to the nomogram while, for the 30–34 age group, differences were not statistically significant despite a trend towards lower values.

Consistent findings were observed when considering only women carrying *BRCA1/2* P/LPVs (overall $p = 0.024$, 25–29 years group $p = 0.008$, shown in Table S1 of Supplementary Materials). Nevertheless, when splitting the *BRCA1/2* population into *BRCA1* and *BRCA2* P/LPV carries, the significant decrease in AMH levels was mostly ascribable to *BRCA1* P/LPV carriers (overall $p = 0.03$), with a significantly lower ovarian reserve in the 20–29 years age group ($p = 0.008$). In *BRCA2* P/LPV carriers, on the other hand, no significant difference was observed compared to the nomogram ($p = 0.312$).

The distribution of AMH levels in women carrying a P/LPV in genes other than *BRCA1/2* is reported in Fig. 2A and Table S2 of Supplementary Materials. However, the sample size is too limited to draw any conclusion.

AFC Evaluation

Eighty-five patients (32 *BRCA1*, 45 *BRCA2*, 8 other genes) had available AFC for the analysis. The overall mean AFC was 16.16 (SD 9.86, median 15), with 16.06 (SD 9.02, median 15) in *BRCA1* P/LPV carriers and 15.98 in *BRCA2* P/LPV carriers (SD 10.73, median 15). No significant difference in mean AFC was identified between *BRCA1* and *BRCA2* P/LPV carriers ($p = 0.971$). In the overall HBOC population, AFC was observed to be significantly higher compared to the general population ($p < 0.001$), particularly between 20 and 34 years of age ($p < 0.001$). From 35 years onwards, HBOC women showed an overdispersion in terms of AFC, with higher occurrence of extreme values, both higher and lower than the expected distribution in the general population ($p = 0.001$) (Table 3, Fig. 1B).

Among 77 *BRCA1/2* P/LPV carriers, AFC was significantly higher up to 34 years ($p < 0.001$). After 35 years of age, in contrast, AFC values were more variable than expected ($p < 0.001$) and decreased faster compared to those reported in the nomogram (shown in Table S3 of Supplementary Materials). Splitting by *BRCA1* and *BRCA2* P/LPV, AFC was significantly higher in both *BRCA1* and *BRCA2* P/LPV carriers ($p < 0.001$ in both *BRCA1* and *BRCA2*).

AFC distribution in women carrying a P/LPV in genes other than *BRCA1/2* is reported in Fig. 2B and Table S3 of Supplementary Materials. However, the sample size is too limited to draw any conclusion.

For both AMH levels and AFC, no significant correlation was observed with BMI or smoking habits. AMH levels and AFC positively correlated both in the whole sample (MD = 0.13, 95%CI:0.11–0.16, $p < 0.001$) and in the *BRCA1/2* subpopulations (*BRCA1*: MD = 0.16, 95%CI:0.10–0.22, $p < 0.001$; *BRCA2*: MD = 0.13, 95%CI:0.10–0.16, $p < 0.001$). Sufficient evidence has not emerged to draw conclusions on the possible effects of *BRCA1/2* P/LPVs on the relationship between AFC and AMH levels.

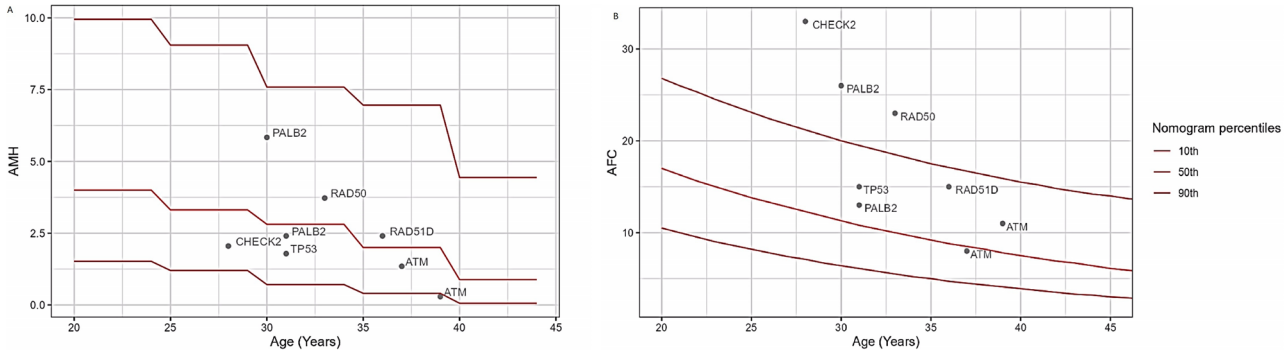

Fig. 2 | Fertility biomarkers in women with P/LPV in genes other than BRCA1/2. A AMH and (**B**) AFC observed vs nomogram curves in women with P/LPV in genes other than *BRCA1/2*. AMH: anti mullerian hormone. AFC antral follicular count.

Table 3 | Distribution of AFC in the HBOC population, *BRCA1* P/LPV carriers and *BRCA2* P/LPV carriers compared with the expected nomogram for the general population

	Percentile Distribution in Study Population (HBOC)					Nomogram				
Age	**0–5**	**5–50**	**50–95**	**95–100**	**Total**	**0–10**	**10–50**	**50–90**	**90–100**	***p-value***
20–29	0 (0%)	8 (29%)	9 (32%)	11 (39%)	28 (100%)	10%	40%	40%	10%	3.36e-6
30–34	0 (0%)	0 (0%)	13 (59%)	9 (41%)	22 (100%)	10%	40%	40%	10%	1.96e-7
≥35	9 (26%)	7 (20%)	12 (34%)	7 (20%)	35 (100%)	10%	40%	40%	10%	0.001
Total	9 (11%)	15 (18%)	34 (40%)	27 (32%)	85 (100%)	10%	40%	40%	10%	5.11e-11
	Percentile Distribution in BRCA1 P/LPV carriers					**Nomogram**				
20–29	0 (0%)	3 (27%)	5 (45%)	3 (27%)	11 (100%)	10%	40%	40%	10%	0.178
30–34	0 (0%)	0 (0%)	4 (44%)	5 (56%)	9 (100%)	10%	40%	40%	10%	3.63e-5
≥35	3 (25%)	1 (8%)	6 (50%)	2 (17%)	12 (100%)	10%	40%	40%	10%	0.088
Total	3 (9%)	4 (13%)	15 (47%)	10 (31%)	32 (100%)	10%	40%	40%	10%	0.0001
	Percentile Distribution in BRCA2 P/LPV carriers					**Nomogram**				
20–29	0 (0%)	5 (31%)	4 (25%)	7 (44%)	16 (100%)	10%	40%	40%	10%	0.0001
30–34	0 (0%)	0 (0%)	7 (78%)	2 (22%)	9 (100%)	10%	40%	40%	10%	0.029
≥35	6 (30%)	5 (25%)	4 (20%)	5 (25%)	20 (100%)	10%	40%	40%	10%	0.001
Total	6 (13%)	10 (22%)	15 (33%)	14 (31%)	45 (100%)	10%	40%	40%	10%	1.89e-5

HBOC hereditary breast and/or ovarian cancer, *P/LPV* pathogenic/likely pathogenic variants.

Discussion

In the last decades, while oncological risks associated with germline P/LPVs in HBOC syndrome-related genes have been extensively studied, little has become known about the non-oncological implications of these genetic alterations, particularly in terms of how these disorders can affect fertility. Moreover, whether patients with *BRCA1/2* germline P/LPVs have a lower ovarian reserve than non-carriers is still an unsolved issue[26–28,45–52]. This hypothesis was firstly put forward based on the observation that *BRCA1/2* P/LPV carriers seemed to have a lower response to gonadotropins during ovarian stimulation for fertility preservation[46,53]. Alterations to these genes can lead to oocyte apoptosis and premature follicular depletion in vitro[28]. In addition, some authors reported that female carriers tend to experience premature menopause, increased ovarian aging, decreased ovarian reserve, and lower ovarian response to ovarian stimulation than non-carriers[27,45].

AMH is currently one of the best biomarkers to predict menopausal age and reproductive life span[37,40,54,55]. AMH is solely produced from granulosa cells of antral follicles. AMH production begins during intrauterine life. It reaches a peak in the mid-20s and then decreases progressively until menopause, when it becomes undetectable[56]. In our study, healthy carriers of HBOC syndrome showed lower AMH levels compared to the nomogram. The decrease in AMH levels was significant starting at 20 to 29 and over 35 of age, but was also present in women aged 30–34 years (lack of statistical significance in this age group could be due to the smaller sample size). Interestingly, splitting the study population into *BRCA1* and *BRCA2* P/LPV carries, these lower values were mostly ascribable to *BRCA1* P/LPV carriers, starting from 20 years of age. Although the available literature is conflicting, these results are in line with two recent meta-analysis showing that women with germline *BRCA1/2* P/LPV had significantly lower AMH levels compared to controls. In these metanalysis as well, AMH levels were lower in women with *BRCA1* P/LPV, but not in *BRCA2* P/LPV carriers, compared to controls[57,58].

Our study also included AFC evaluation. In our analysis, AFC was significantly higher up to 34 years, but it decreased faster than that in the general population after 35 years of age. Higher overall AFC may reflect a higher sensitivity of current instruments for TV-US, compared to those available when the nomogram was defined[43]. Even taking this bias into account, however, the significant decrease in AFC after 35 years of age corroborates the hypothesis that ovarian reserve in HBOC syndrome decreases significantly and faster than in the general population.

As in the general population, AMH and AFC were found to be positively correlated both in the whole sample and in the *BRCA1/2* subpopulations. Nevertheless, the mean difference between the two was lower than in the previous literature[59,60]. Whether this means that the relationship between AFC and AMH is less strong in *BRCA1/2*P/LPV carriers should be investigated in future research. *BRCA1* and *BRCA2* play a key role in DNA double-strand break (DSB) repair through homologous recombination, as well as in chromosomal stability, apoptosis, and cell cycle[61]. Moreover, other genes belonging to the

homologous recombination pathway have been identified as predisposing factors to premature ovarian insufficiency, such as *ATM* bi-allelic mutation[62]. In humans, oocyte meiosis starts during embryogenesis and concludes many years later. Oocyte meiosis has a long stop at the stage of meiosis I, ranging from fetal life to even several decades after ovulation. In this context, the accumulation of DSBs and the role of *BRCA1* and *BRCA2* in maintaining chromosome telomere integrity can be associated with ovarian aging and reproductive senescence[48,63–66]. Therefore, the role of *BRCA1* in the DSB repair mechanism could be at the basis of the lower ovarian reserve in *BRCA1* P/LPV carriers. It remains to be fully elucidated why the same process seems not to affect *BRCA2* P/LPV carriers.

Several studies indicated that *BRCA1/2*P/LPVs carriers experience early menopause[27,45,47], nevertheless, menstruation in not the finest indicator of ovarian reserve and may be influenced by other conditions. Overall, the possible modest reduction in ovarian reserve in *BRCA1/2*P/LPVs carriers and the likely earlier onset of menopause seems not to impact on natural fertility. Indeed, no difference was found regarding parity and the use of assisted reproductive techniques between *BRCA1/2* P/LPVs carriers and general populations, indicating normal fertility in *BRCA1/2* P/LPVs carriers[50,67–70]. Finally, the rate of spontaneous termination of pregnancy in our HBOC population was in line with the previous literature[71].

To our knowledge, this is one of the largest studies including healthy women with P/LPVs in breast and/or ovarian cancer predisposition genes. At the same time, it is the first study to also include high and moderate penetrant genes defining HBOC syndrome, other than *BRCA1/2*. Moreover, all women in our study were prospectively examined by the same gynecologist (G.S.), AMH was assayed at the same laboratory, and fertility evaluation also included AFC, along with AMH. In addition, all women enrolled were under no hormonal contraceptive methods at the time of evaluation. Nonetheless, our analysis presents some limitations. In particular, our study lacks a control group. Our results have, therefore, been compared with previously published nomograms. In addition, the sample size of women with P/LPV in genes other than *BRCA1/2* is still too limited to drive any conclusion from this subset.

It is important to underline that lower AMH values in *BRCA1/2* P/LPV carriers do not translate into less fertility. Such values, however, result in a shorter reproductive window in a lifetime. Our study underlines the importance of counseling, so that young healthy carriers do not delay pregnancy, especially with a *BRCA1* P/LPV. Furthermore, it is crucial to evaluate the possibility of oocyte cryopreservation at a younger age and in elective settings, when ovarian stimulation may yield more better-quality oocytes. In addition, due to the possible existence of poor ovarian reserve as well as DNA damage-induced follicle death, it can be hypothesized that *BRCA1/2* P/LPV carriers may be at a higher risk of chemo-induced amenorrhea during chemotherapy[46]. It has already been reported that chemotherapy induces DNA DSBs both in mice[72–74] and in human oocytes[75–77], therefore, *BRCA1/2* P/LPVs carriers are potentially more sensitive to gonadotoxicity of chemotherapy compared to non-carriers. Particularly, higher gonadotoxicity has been reported with alkylating and platinum-based agents, taxanes, anthracyclines, topoisomerase inhibitors and vinca alkaloids[78]. The impact of endocrine therapies (including tamoxifen) on fertility in *BRCA1/2* P/LPVs carriers are still conflicting[79–81], whereas data on new therapies developed for *BRCA1/2* P/LPVs patients (including PARP inhibitors) are substantially lacking[32]. As a result, *BRCA1/2* P/LPV carriers should be counseled for ovarian suppression and preservation before the start of any oncological treatment.

To conclude, as previously highlighted by Peccatori et al.[30], the fertility issues that *BRCA* patients may face, lead to some considerations: (1) the evidence on a shortening of reproductive life and a possible premature diminishing of ovarian reserve in BRCA P/LPVs carriers are increasing; (2) when the risk-reducing bilateral salpingo-oophorectomy is chosen at 35 years old, oocyte cryopreservation prior to surgery should be considered; (3) a policy of oocyte cryopreservation in young carriers before cancer development deserves consideration. Particularly, fertility preservation strategies should be considered at a young age and in an elective setting, when ovarian stimulation may yield more oocytes of better quality. (4) Preimplantation genetic diagnosis (PGD) may be considered since it could avoid the possibility of transmitting the mutation to the offspring[30,31]. Our study confirms a consistent trend for reduced reproductive potential in young healthy women carrying germline P/LPVs in genes associated with HBOC syndrome, particularly in *BRCA1* P/LPV carriers. These findings need to be confirmed by larger studies that also include carriers of germline P/LPVs in other tumor suppressor genes, since these may influence fertility counseling for this specific women population.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Azienda Ospedaliero-Universitaria di Modena. The source data for Figs. 1, 2 can be found in Supplementary Data 1 (for Fig. 1) and Supplementary Data 2 (for Fig. 2).

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References

1. Kuchenbaecker, K. B. et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* **317**, 2402–2416 (2017).
2. National Comprehensive Cancer Network, V. 2. 2024. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (2023).
3. Sessa, C. et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann. Oncol.* **34**, 33–47 (2023).
4. Bedrosian, I. et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. *J Clin Oncol* JCO2302225. https://doi.org/10.1200/JCO.23.02225 (2024).
5. Cortesi, L. et al. A rapid genetic counselling and testing in newly diagnosed breast cancer is associated with high rate of risk-reducing mastectomy in BRCA1/2-positive Italian women. *Ann. Oncol.* **25**, 57–63 (2014).
6. Cortesi, L. et al. Evaluation of Transvaginal Ultrasound plus CA-125 Measurement and Prophylactic Salpingo-Oophorectomy in Women at Different Risk Levels of Ovarian Cancer: The Modena Study Group Cohort Study. *Oncology* **93**, 377–386 (2017).
7. Razzaboni, E. et al. Acceptability and adherence in a chemoprevention trial among women at increased risk for breast cancer attending the Modena Familial Breast and Ovarian Cancer Center (Italy). *Breast J.* **19**, 10–21 (2013).
8. Toss, A. et al. The impact of reproductive life on breast cancer risk in women with family history or BRCA mutation. *Oncotarget* **8**, 9144–9154 (2017).
9. Blondeaux, E. et al. Germline TP53 pathogenic variants and breast cancer: A narrative review. *Cancer Treat. Rev.* **114**, 102522 (2023).
10. Toss, A. et al. Cancer Predisposition Genes in Adolescents and Young Adults (AYAs): a Review Paper from the Italian AYA Working Group. *Curr. Oncol. Rep.* **24**, 843–860 (2022).
11. Grandi, G. et al. The challenging screen detection of ovarian cancer in BRCA mutation carriers adhering to a 6-month follow-up program: results from a 6-years surveillance. *Menopause* **29**, 63–72 (2021).
12. Toss, A. et al. Clinicopathologic Profile of Breast Cancer in Germline ATM and CHEK2 Mutation Carriers. *Genes* **12**, 616 (2021).
13. Grandi, G. et al. Prophylactic risk-reducing salpingo-oophorectomy in BRCA mutation carriers: what is going on in a region of northern Italy? *Maturitas* **143**, 59–64 (2021).
14. Piombino, C. et al. Secondary Prevention in Hereditary Breast and/or Ovarian Cancer Syndromes Other Than BRCA. *J. Oncol.* **2020**, 1–10 (2020).

15. Dullens, B. et al. Cancer Surveillance in Healthy Carriers of Germline Pathogenic Variants in BRCA1/2: A Review of Secondary Prevention Guidelines. *J. Oncol.* **2020**, 9873954 (2020).
16. Grandi, G., Sammarini, M., Del Savio, M. C., Toss, A. & Facchinetti, F. Combined hormonal contraceptives in BRCA gene mutation carriers: why not? *Eur. J. Contracept. Reprod. Health Care* **24**, 417–419 (2019).
17. Grandi, G. et al. Primary fallopian tube carcinoma (PFTC) in a BRIP-1 mutation carrier: the first case report. *Fam. Cancer* **19**, 291–295 (2020).
18. Toss, A. et al. Hereditary ovarian cancers: state of the art. *Minerva Med.* **110**, 301–319 (2019).
19. Cortesi, L., Piombino, C. & Toss, A. Germline Mutations in Other Homologous Recombination Repair-Related Genes Than BRCA1/2: Predictive or Prognostic Factors? *JPM* **11**, 245 (2021).
20. Toss, A. et al. BRCA Detection Rate in an Italian Cohort of Luminal Early-Onset and Triple-Negative Breast Cancer Patients without Family History: When Biology Overcomes Genealogy. *Cancers* **12**, 1252 (2020).
21. Nappi, R. E., Cassani, C., Rossi, M., Zanellini, F. & Spinillo, A. Dealing with premature menopause in women at high-risk for hereditary genital and breast cancer. *Minerva Ginecol.* **68**, 602–612 (2016).
22. Stuursma, A., van Driel, C. M. G., Wessels, N. J., de Bock, G. H. & Mourits, M. J. E. Severity and duration of menopausal symptoms after risk-reducing salpingo-oophorectomy. *Maturitas* **111**, 69–76 (2018).
23. Philp, L. et al. Patient reported outcomes after risk-reducing surgery in patients at increased risk of ovarian cancer. *Gynecol. Oncol.* **164**, 421–427 (2022).
24. Kiebert, G. M., de Haes, J. C. & van de Velde, C. J. The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. *J. Clin. Oncol.* **9**, 1059–1070 (1991).
25. Scotto, L., Pizzoli, S. F. M., Marzorati, C., Mazzocco, K. & Pravettoni, G. The impact of prophylactic mastectomy on sexual well-being: a systematic review. *Sex. Med Rev.* **12**, 164–177 (2024).
26. Lambertini, M. et al. Fertility and pregnancy issues in BRCA-mutated breast cancer patients. *Cancer Treat. Rev.* **59**, 61–70 (2017).
27. Finch, A. et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. *Fertil. Steril.* **99**, 1724–1728 (2013).
28. Wang, E. T. et al. BRCA1 germline mutations may be associated with reduced ovarian reserve. *Fertil. Steril.* **102**, 1723–1728 (2014).
29. Corrado, G., Marchetti, C., Trozzi, R., Scambia, G. & Fagotti, A. Fertility preservation in patients with BRCA mutations or Lynch syndrome. *Int J. Gynecol. Cancer* **31**, 332–338 (2021).
30. Peccatori, F. A. et al. Fertility preservation in women harboring deleterious BRCA mutations: ready for prime time? *Hum. Reprod.* **33**, 181–187 (2018).
31. Laot, L. et al. Should Preimplantation Genetic Testing (PGT) Systematically Be Proposed to BRCA Pathogenic Variant Carriers? *Cancers* **14**, 5769 (2022).
32. Dias Nunes, J., Demeestere, I. & Devos, M. BRCA Mutations and Fertility Preservation. *IJMS* **25**, 204 (2023).
33. Vigier, B., Tran, D., Legeai, L., Bezard, J. & Josso, N. Origin of anti-Mullerian hormone in bovine freemartin fetuses. *Reproduction* **70**, 473–479 (1984).
34. La Marca, A. et al. Anti-Mullerian Hormone in Premenopausal Women and After Spontaneous or Surgically Induced Menopause. *J. Soc. Gynecol. Investig.* **12**, 545–548 (2005).
35. La Marca, A. & Volpe, A. Anti-Müllerian hormone (AMH) in female reproduction: is measurement of circulating AMH a useful tool? *Clin. Endocrinol.* **64**, 603–610 (2006).
36. Van Disseldorp, J. et al. Relationship of Serum Antimüllerian Hormone Concentration to Age at Menopause. *J. Clin. Endocrinol. Metab.* **93**, 2129–2134 (2008).
37. Tehrani, F. R., Solaymani-Dodaran, M., Tohidi, M., Gohari, M. R. & Azizi, F. Modeling age at menopause using serum concentration of anti-mullerian hormone. *J. Clin. Endocrinol. Metab.* **98**, 729–735 (2013).
38. Gougeon, A. Ovarian follicular growth in humans: ovarian ageing and population of growing follicles. *Maturitas* **30**, 137–142 (1998).
39. Broekmans, F. J., Faddy, M. J., Scheffer, G. & Te Velde, E. R. Antral follicle counts are related to age at natural fertility loss and age at menopause. *Menopause* **11**, 607–614 (2004).
40. Broer, S. L. et al. Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. *J. Clin. Endocrinol. Metab.* **96**, 2532–2539 (2011).
41. Wellons, M. F. et al. Antral follicle count predicts natural menopause in a population-based sample: the Coronary Artery Risk Development in Young Adults Women's Study. *Menopause* **20**, 825–830 (2013).
42. Bharucha, P. P. et al. Genetic Testing and Screening Recommendations for Patients with Hereditary Breast Cancer. *RadioGraphics* **40**, 913–936 (2020).
43. Bozdag, G., Calis, P., Zengin, D., Tanacan, A. & Karahan, S. Age related normogram for antral follicle count in general population and comparison with previous studies. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **206**, 120–124 (2016).
44. La Marca, A., Tolani, A. D. & Capuzzo, M. The interchangeability of two assays for the measurement of anti-Müllerian hormone when personalizing the dose of FSH in in-vitro fertilization cycles. *Gynecol. Endocrinol.* **37**, 372–376 (2021).
45. Rzepka-Górska, I. et al. Premature menopause in patients with BRCA1 gene mutation. *Breast Cancer Res. Treat.* **100**, 59–63 (2006).
46. Oktay, K., Cil, A. P. & Zhang, J. Who is the best candidate for oocyte cryopreservation research? *Fertil. Steril.* **93**, 13–15 (2010).
47. Lin, W. T. 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).
48. Titus, S. et al. Impairment of BRCA1-Related DNA Double-Strand Break Repair Leads to Ovarian Aging in Mice and Humans. *Sci. Transl. Med*. **5**, (2013).
49. Giordano, S. 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).
50. Pal, T., Keefe, D., Sun, P. & Narod, S. A. Fertility in women with BRCA mutations: a case-control study. *Fertil. Steril.* **93**, 1805–1808 (2010).
51. Michaelson-Cohen, R. et al. BRCA Mutation Carriers Do Not Have Compromised Ovarian Reserve. *Int J. Gynecol. Cancer* **24**, 233–237 (2014).
52. Van Tilborg, T. C. et al. Serum AMH levels in healthy women from *BRCA1/2* mutated families: are they reduced? *Hum. Reprod.* **31**, 2651–2659 (2016).
53. Turan, V., Quinn, M. M., Dayioglu, N., Rosen, M. P. & Oktay, K. The impact of malignancy on response to ovarian stimulation for fertility preservation: a meta-analysis. *Fertil. Steril.* **110**, 1347–1355 (2018).
54. Sowers, M. R. et al. Anti-mullerian hormone and inhibin B in the definition of ovarian aging and the menopause transition. *J. Clin. Endocrinol. Metab.* **93**, 3478–3483 (2008).
55. Anderson, R. A. et al. Anti-Müllerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer: a systematic review. *Hum. Reprod. Update* **28**, 417–434 (2022).
56. Kelsey, T. W., Wright, P., Nelson, S. M., Anderson, R. A. & Wallace, W. H. B. A validated model of serum anti-müllerian hormone from conception to menopause. *PLoS One* **6**, e22024 (2011).
57. Gasparri, M. L. et al. Ovarian reserve of women with and without BRCA pathogenic variants: A systematic review and meta-analysis. *Breast* **60**, 155–162 (2021).

58. Turan, V. et al. Association of Germline BRCA Pathogenic Variants With Diminished Ovarian Reserve: A Meta-Analysis of Individual Patient-Level Data. *J. Clin. Oncol.* **39**, 2016–2024 (2021).
59. Bentzen, J. G. et al. Ovarian antral follicle subclasses and anti-mullerian hormone during normal reproductive aging. *J. Clin. Endocrinol. Metab.* **98**, 1602–1611 (2013).
60. Hansen, K. R., Hodnett, G. M., Knowlton, N. & Craig, L. B. Correlation of ovarian reserve tests with histologically determined primordial follicle number. *Fertil. Steril.* **95**, 170–175 (2011).
61. Piombino, C. & Cortesi, L. Insights into the Possible Molecular Mechanisms of Resistance to PARP Inhibitors. *Cancers* **14**, 2804 (2022).
62. Turan, V. & Oktay, K. BRCA-related ATM-mediated DNA double-strand break repair and ovarian aging. *Hum. Reprod. Update* **26**, 43–57 (2020).
63. Oktay, K., Turan, V., Titus, S., Stobezki, R. & Liu, L. BRCA Mutations, DNA Repair Deficiency, and Ovarian Aging. *Biol. Reprod.* **93**, 67 (2015).
64. Foulkes, W. D. & Shuen, A. Y. In brief: BRCA1 and BRCA2. *J. Pathol.* **230**, 347–349 (2013).
65. Subramanian, V. V. & Hochwagen, A. The meiotic checkpoint network: step-by-step through meiotic prophase. *Cold Spring Harb. Perspect. Biol.* **6**, a016675 (2014).
66. Kalmbach, K. H. et al. Telomeres and human reproduction. *Fertil. Steril.* **99**, 23–29 (2013).
67. Gal, I. et al. Offspring Gender Ratio and the Rate of Recurrent Spontaneous Miscarriages in Jewish Women at High Risk for Breast/Ovarian Cancer. *Am. J. Hum. Genet.* **74**, 1270–1275 (2004).
68. Smith, K. R., Hanson, H. A., Mineau, G. P. & Buys, S. S. Effects of *BRCA1* and *BRCA2* mutations on female fertility. *Proc. R. Soc. B.* **279**, 1389–1395 (2012).
69. Moslehi, R., Singh, R., Lessner, L. & Friedman, J. M. Impact of BRCA mutations on female fertility and offspring sex ratio. *Am. J. Hum. Biol.* **22**, 201–205 (2010).
70. Kwiatkowski, F. et al. BRCA Mutations Increase Fertility in Families at Hereditary Breast/Ovarian Cancer Risk. *PLoS One* **10**, e0127363 (2015).
71. García-Enguídanos, A., Calle, M. E., Valero, J., Luna, S. & Domínguez-Rojas, V. Risk factors in miscarriage: a review. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **102**, 111–119 (2002).
72. Roti Roti, E. C., Leisman, S. K., Abbott, D. H. & Salih, S. M. Acute doxorubicin insult in the mouse ovary is cell- and follicle-type dependent. *PLoS One* **7**, e42293 (2012).
73. Nguyen, Q. N. et al. Cisplatin- and cyclophosphamide-induced primordial follicle depletion is caused by direct damage to oocytes. *Mol. Hum. Reprod.* **25**, 433–444 (2019).
74. Nguyen, Q. N., Zerafa, N., Findlay, J. K., Hickey, M. & Hutt, K. J. DNA repair in primordial follicle oocytes following cisplatin treatment. *J. Assist. Reprod. Genet* **38**, 1405–1417 (2021).
75. Winship, A. L., Stringer, J. M., Liew, S. H. & Hutt, K. J. The importance of DNA repair for maintaining oocyte quality in response to anti-cancer treatments, environmental toxins and maternal ageing. *Hum. Reprod. Update* **24**, 119–134 (2018).
76. Soleimani, R., Heytens, E., Darzynkiewicz, Z. & Oktay, K. Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise. *Aging* **3**, 782–793 (2011).
77. Oktay, K. H. 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).
78. Spears, N. et al. Ovarian damage from chemotherapy and current approaches to its protection. *Hum. Reprod. Update* **25**, 673–693 (2019).
79. Ghunaim, S., Ghazeeri, G., Khalife, D. & Azim, H. A. Fertility preservation in patients with BRCA mutation. *Ecancermedicalscience* **14**, 1033 (2020).
80. Partridge, A. H. et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil. Steril.* **94**, 638–644 (2010).
81. Shandley, L. M. et al. Impact of tamoxifen therapy on fertility in breast cancer survivors. *Fertil. Steril.* **107**, 243–252.e5 (2017).

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Author contributions

Concept and design: G.S., G.G., A.T. Acquisition, analysis, or interpretation of data: G.S., E.B., M.V., C.M., R.L.B., R.C.C., R.D., E.T. Drafting of the manuscript: G.S., A.T., C.P. Critical review of the manuscript for important intellectual content: M.L., F.A.P., M.D., L.C., A.L.M. Statistical analysis: R.C.C., R.D. Obtained funding: A.T. Administrative, technical, or material support: G.S., C.M., R.L.B. Supervision: G.S., A.T.

Competing interests

G.S., G.G., M.V., C.P., C.M., R.L.B., R.C.C., R.D., F.A.P., and M.D. reported no conflicts of interest. E.B. reported travel grants from Lilly, Novartis, Pfizer, MSD, AstraZeneca, Gilead, and Daiichi Sankyo, all outside the submitted work. M.L. reported advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Knight, Ipsen, AstraZeneca; travel grants from Gilead, Daiichi Sankyo, Roche and a research grant (to his Institution) from Gilead, all outside the submitted work. E.T. reported travel grants and speaker honoraria from MSD and SOPHiA GENETICS, all outside the submitted work. L.C. reported personal fees from AstraZeneca, Pfizer, Novartis, Gilead, and Clovis and grants from MSD outside the submitted work. A.L.M. reported grants from Merck, Ferring Pharmaceuticals, MSD, IBSA MSD, Roche Diagnostics, Beckmann Coulter, and TEVA, all outside the submitted work. A.T. reported conflicts of interest with Lilly, Novartis, Pfizer, AstraZeneca, MSD, Seagen, Gilead, and Daiichi Sankyo, all outside the submitted work.

Additional information

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