RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

INSTITUT NATIONAL DU CANCER

Fertilité des femmes porteuses d'une mutation BRCA1 présentant un cancer du sein

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agence de la biomédecine
Du don à la vie

PARIS | 3 DÉCEMBRE 2024
SÉMINAIRE RECHERCHE EN PRÉSERVATION DE LA FERTILITÉ CHEZ LES PATIENTS ATTEINTS D'UN CANCER

Fertility after breast cancer

"Fertility and pregnancy-related issues are one of the top three priorities for young women with breast cancer"

At time of decision making about treatment, concerned about fertility		
Not at all	301	49
A little	83	13
Somewhat	88	14
Very	148	24

→ ≈ 50%

Characteristic	Total Sample, n=918	Type of Cancer				
		Leukemia, n=121	Hodgkin Disease, n=286[a]	Non-Hodgkin Lymphoma, n=169[a]	Breast Cancer, n=223	Gastrointestinal Cancer, n=108
Age at diagnosis, y, mean (SD)	31.5 (6.7)	28.3 (7.2)	27.9 (6.2)	31.6 (6.0)	36.3 (4.0)	34.9 (4.6)
Age at survey, y, mean (SD)	40.9 (8.4)	37.0 (8.3)	36.5 (8.0)	40.5 (7.1)	47.1 (5.9)	44.6 (6.2)
Years since diagnosis, mean (SD)	9.6 (4.4)	8.7 (4.3)	8.6 (4.4)	8.9 (3.9)	10.8 (4.5)	9.7 (4.0)
Children before treatment, No. (%)	476 (52%)	46 (38%)	105 (37%)	88 (52%)	163 (73%)	76 (70%)
Desiring children after treatment, No. (%)	504 (54%)	71 (59%)	181 (63%)	82 (49%)	104 (47%)	61 (56%)

Ruddy KJ et al, J Clin Oncol 2014;32:1151-1156. Letourneau JM et al, Cancer 2012;118:1710-7

Risk of POI after (neo)adjuvant therapy

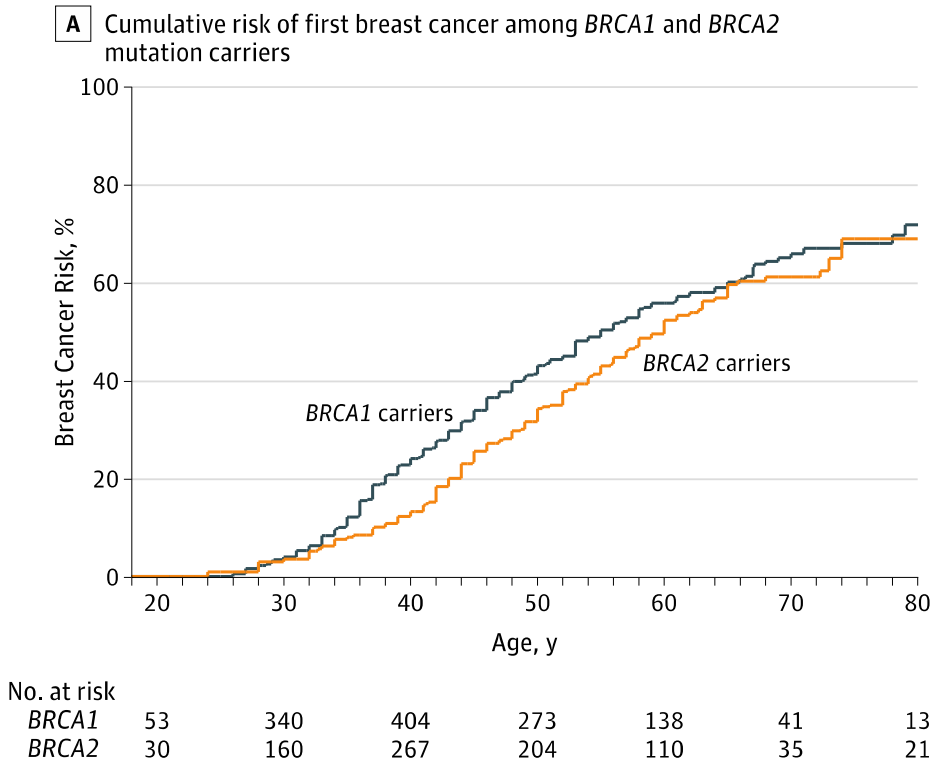
Table 3. Risks of treatment-related amenorrhoea in female patients[a]

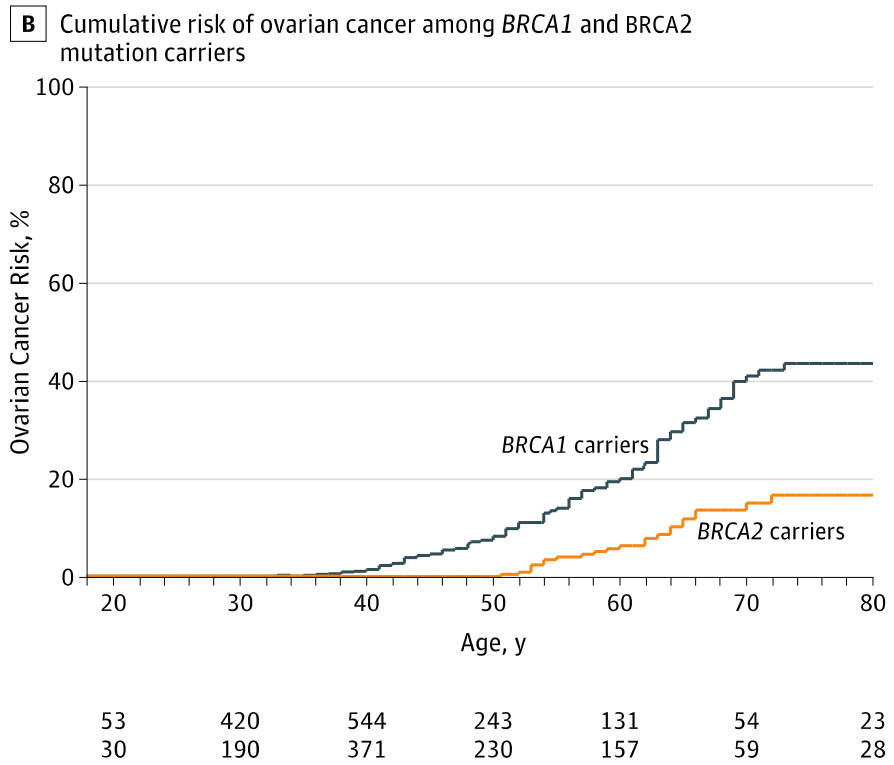
Degree of risk	Treatment type/regimen	Comments
High risk (>80%)	Haematopoietic stem cell transplantation (especially alkylating agent-based myeloablative conditioning with cyclophosphamide, busulfan, melphalan or total body RT)	
	EBRT >6 Gy to a field including the ovaries	
	6 cycles of CMF, CEF, CAF or TAC in women of ≥40 years	Significant decline in AMH levels after treatment Early menopause
	6–8 cycles of escalated BEACOPP in women of ≥30 years	Significant decline in AMH levels after treatment
Intermediate risk (20%–80%)	6 cycles of CMF, CEF, CAF or TAC in women of 30–39 years	Significant decline in AMH levels after treatment Early menopause
	4 cycles of AC in women of ≥40 years	Significant decline in AMH levels after treatment
	4 cycles of AC/EC → taxane	Significant decline in AMH levels after treatment
	4 cycles of dd (F)EC → dd taxane	
	6–8 cycles of escalated BEACOPP in women of <30 years	Significant decline in AMH levels after treatment
	6 cycles of CHOP in women of ≥35 years	Early menopause
	6 cycles of DA-EPOCH in women of ≥35 years	Significant decline in AMH levels after treatment
	FOLFOX in women of ≥40 years	
Low risk (<20%)	6 cycles of CMF, CEF, CAF or TAC in women of <30 years	Significant decline in AMH levels after treatment Early menopause
	4 cycles of AC in women of <40 years	Significant decline in AMH levels after treatment
	2 cycles of escalated BEACOPP	Significant decline in AMH levels after treatment
	ABVD	Insignificant decline in AMH levels after treatment
	6 cycles of CHOP in women of <35 years	Early menopause
	6 cycles of DA-EPOCH in women of <35 years	Significant decline in AMH levels after treatment
	AML therapy (anthracycline/cytarabine)	Insignificant decline in AMH levels after treatment
	ALL therapy (multi-agent)	Insignificant decline in AMH levels after treatment
	Multi-agent ChT for osteosarcoma (doxorubicin, cisplatin, methotrexate, ifosfamide) in women of <35 years	
	Multi-agent ChT for Ewing's sarcoma (doxorubicin, vincristine, dactinomycin, cyclophosphamide, ifosfamide, etoposide) in women of <35 years	
	FOLFOX in women of ≤40 years	
	Antimetabolites and vinca alkaloids	
	BEP or EP in women of <30 years	
	Radioactive iodine (I-131)	Decline in AMH levels after treatment
	Bevacizumab	
Unknown risk	Platinum- and taxane-based ChT	
	Most targeted therapies (including monoclonal antibodies and small molecules)	
	Immunotherapy	

Lambertini et al 2020

BRCA mutation in Breast Cancer patients

Risk of breast and ovarian cancers





72% in BRCA1 mutation carrier

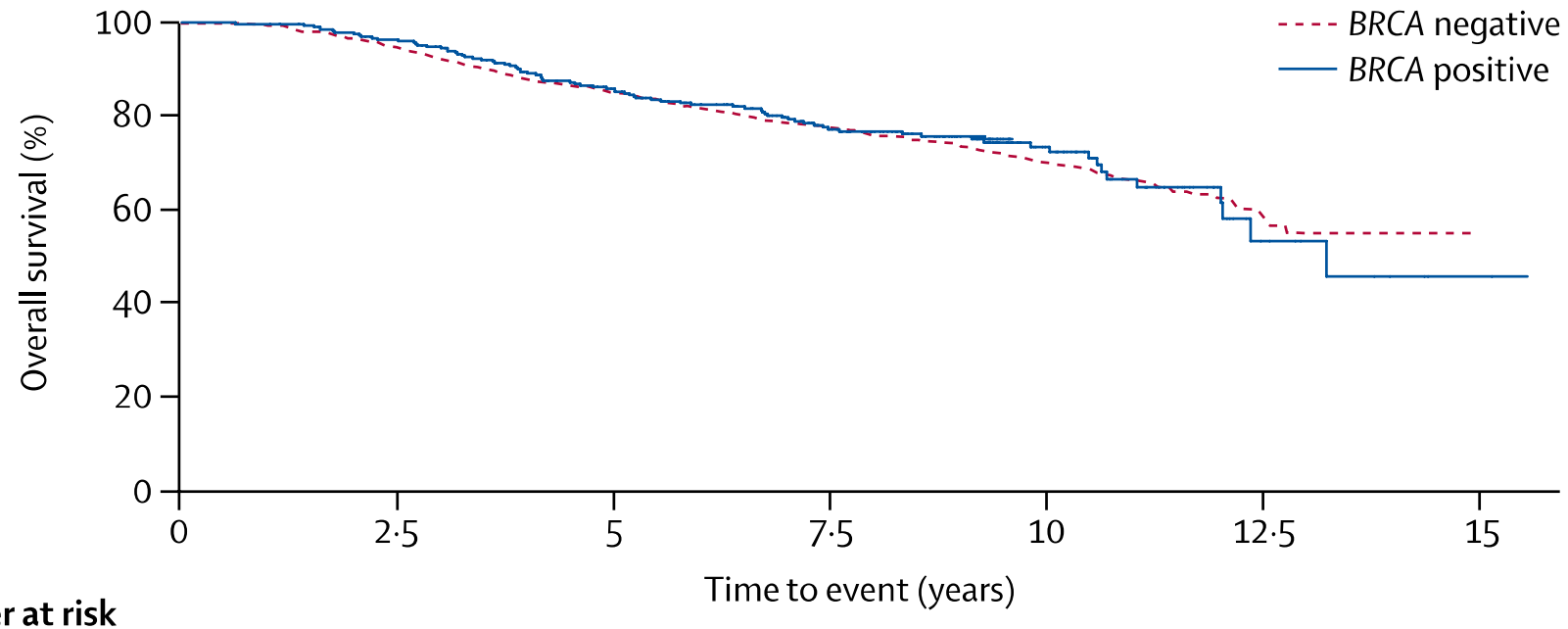
69% in BRCA2 mutation carrier

Kuchenbaecker et al, 2017 JAMA

Kuchenbaecker et al, 2017 JAMA

Outcomes of BRCA mutated patients

A

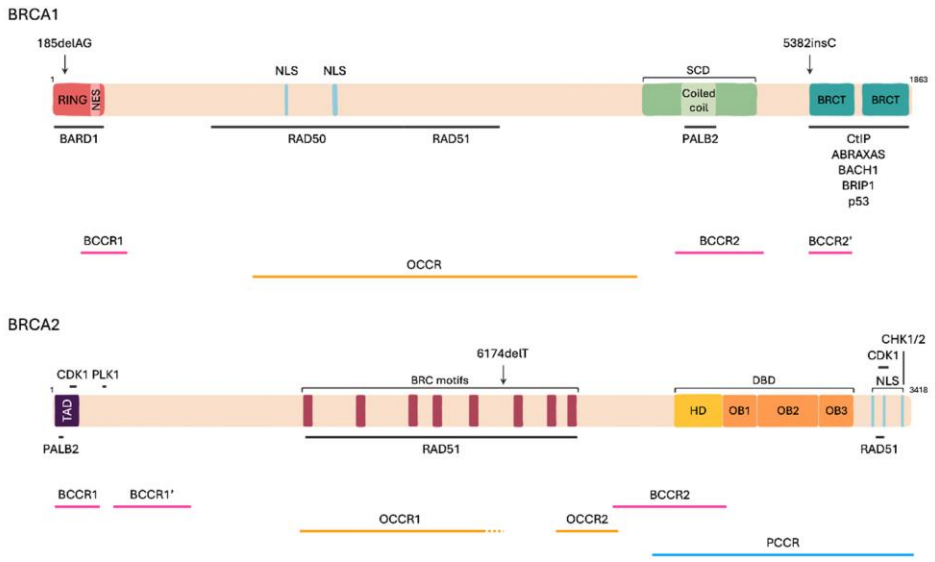


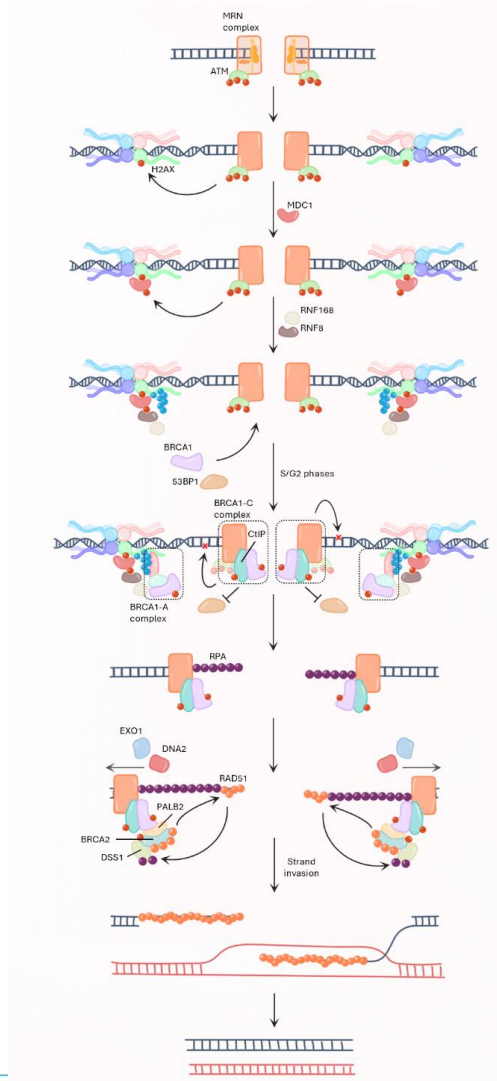
Number at risk (number censored)							
BRCA negative	2395 (125)	2217 (217)	1805 (141)	1160 (78)	452 (30)	48 (3)	0 (0)
BRCA positive	338 (13)	313 (38)	245 (18)	163 (5)	71 (9)	10 (1)	2 (0)

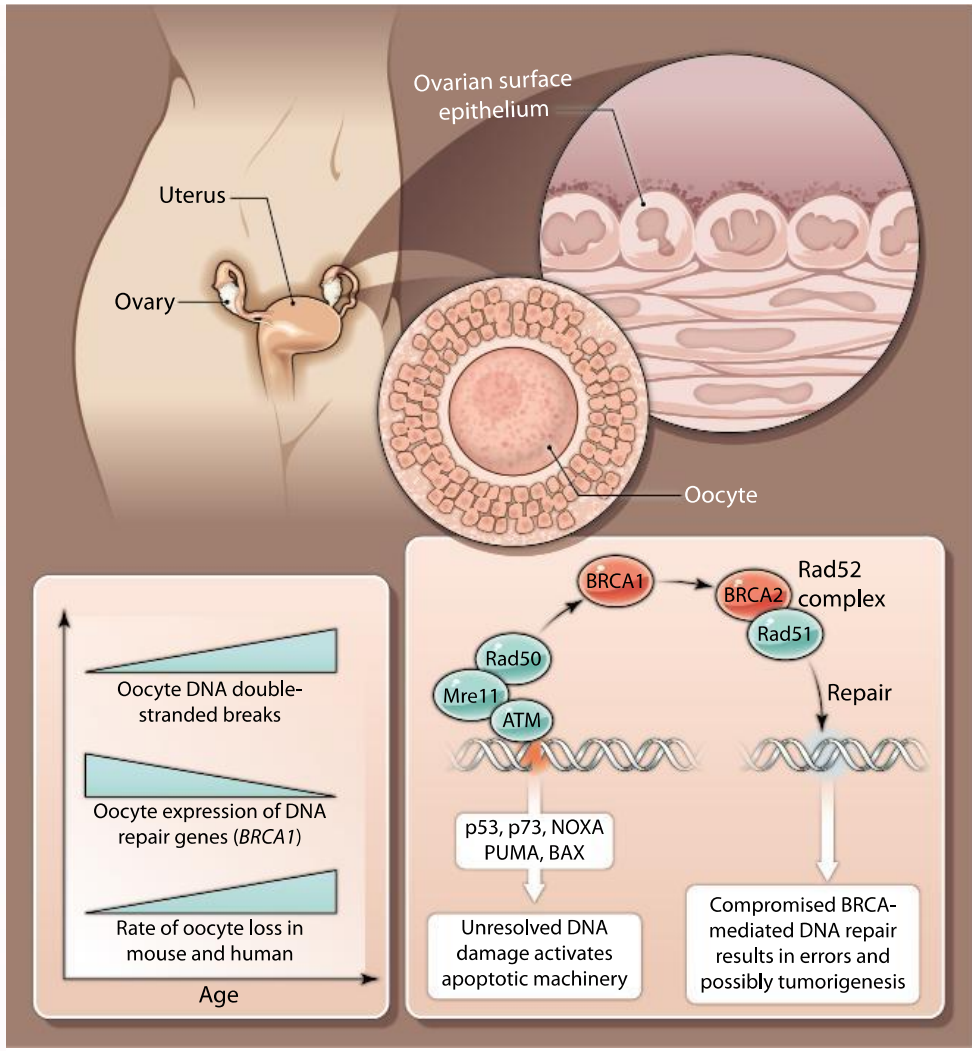
POSH Cohort Study Copson et al , 2018, Lancet

BRCA and Reproduction

DNA Repair (DDR)
Homologous recombination



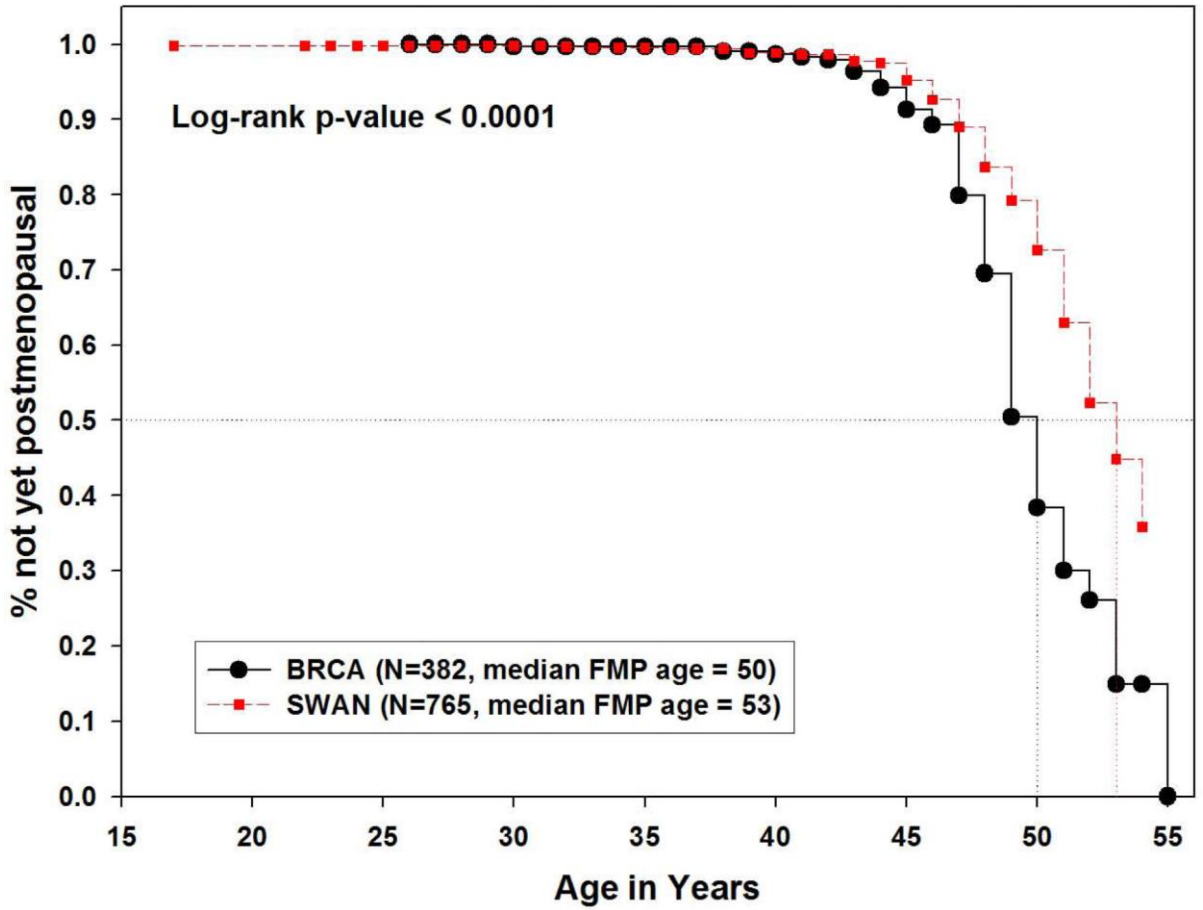




Dias Nunes et al 2023, Titus et al 2013

Impact on ovarian function

- Most of the studies in human did not show any difference in fertility potential between BRCA carriers and non carriers but menopause occurs at earlier age



Lin et al , 2013 Cancer

Specific questions related to BRCA mutation and fertility

- Is pregnancy affect the oncological outcomes in breast cancer?
- Is the BRCA mutation affect the ovarian reserve and fertility preservation performance?
- Does ovarian stimulation safe in BRCA1 carriers?
- Does ART after breast cancer influence the prognosis in BC survivors?
- Does it impact the chemotherapy-induced ovarian damage? -new therapy?

Is Pregnancy safe in breast cancer patients harbouring BRCA mutation?

RBMO

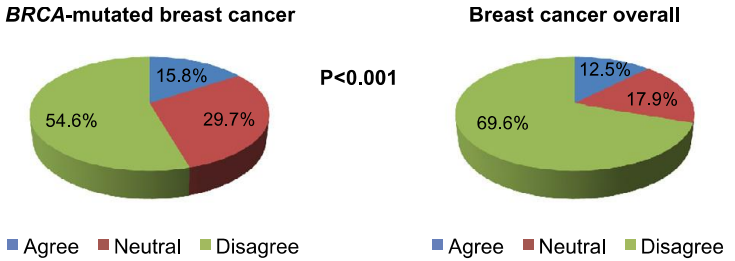
ELSEVIER

ARTICLE

Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients

Matteo Lambertini[1,2,*], Massimo Di Maio[3], Francesca Poggio[4], Olivia Pagani[5], Giuseppe Curigliano[6], Lucia Del Mastro[2,4], Shani Paluch-Shimon[7], Sibylle Loibl[8], Ann H Partridge[9], Hatem A AzimJr[10], Fedro A Peccatori[11,#], Isabelle Demeestere[12,#]

Pregnancy in BC survivors:



OS should not be considered as safe in BRCA-mutated BC survivors for 15.4 % of the physicians ....

Pregnancy After Breast Cancer in Young *BRCA* Carriers

An International Hospital-Based Cohort Study

Lambertini et al 2024, JAMA

Of 4732 *BRCA* carriers included, 659 had at least 1 pregnancy after breast cancer

Variables	No. of patients/No. of events	Univariate hazard ratio (95% CI)	*P* value	Multivariate hazard ratio (95% CI)	*P* value
Study group	4732/1683	0.97 (0.82-1.15)	.74	0.99 (0.81-1.20)	.90
Specific *BRCA* gene					
BRCA1	3033/1101	0.79 (0.64-0.97)	<.001[a]	0.80 (0.63-1.01)	.007[a]
BRCA2	1663/569	1.61 (1.22-2.12)		1.55 (1.12-2.16)	
BRCA1 and *BRCA2*	26/11	1.82 (0.33-10.1)		4.49 (0.28-72.17)	
BRCA, unknown if *BRCA1* or *BRCA2*	10/2	1.11 (0.05-23.2)		NE	

SPECIAL ARTICLE

Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines†

M. Lambertini[1,2], F. A. Peccatori[3], I. Demeestere[4], F. Amant[5,6], C. Wyns[7], J.-B. Stukenborg[8], S. Paluch-Shimon[9], M. J. Halaska[10], C. Uzan[11], J. Meissner[12], M. von Wolff[13], R. A. Anderson[14] & K. Jordan[12], on behalf of the ESMO Guidelines Committee*

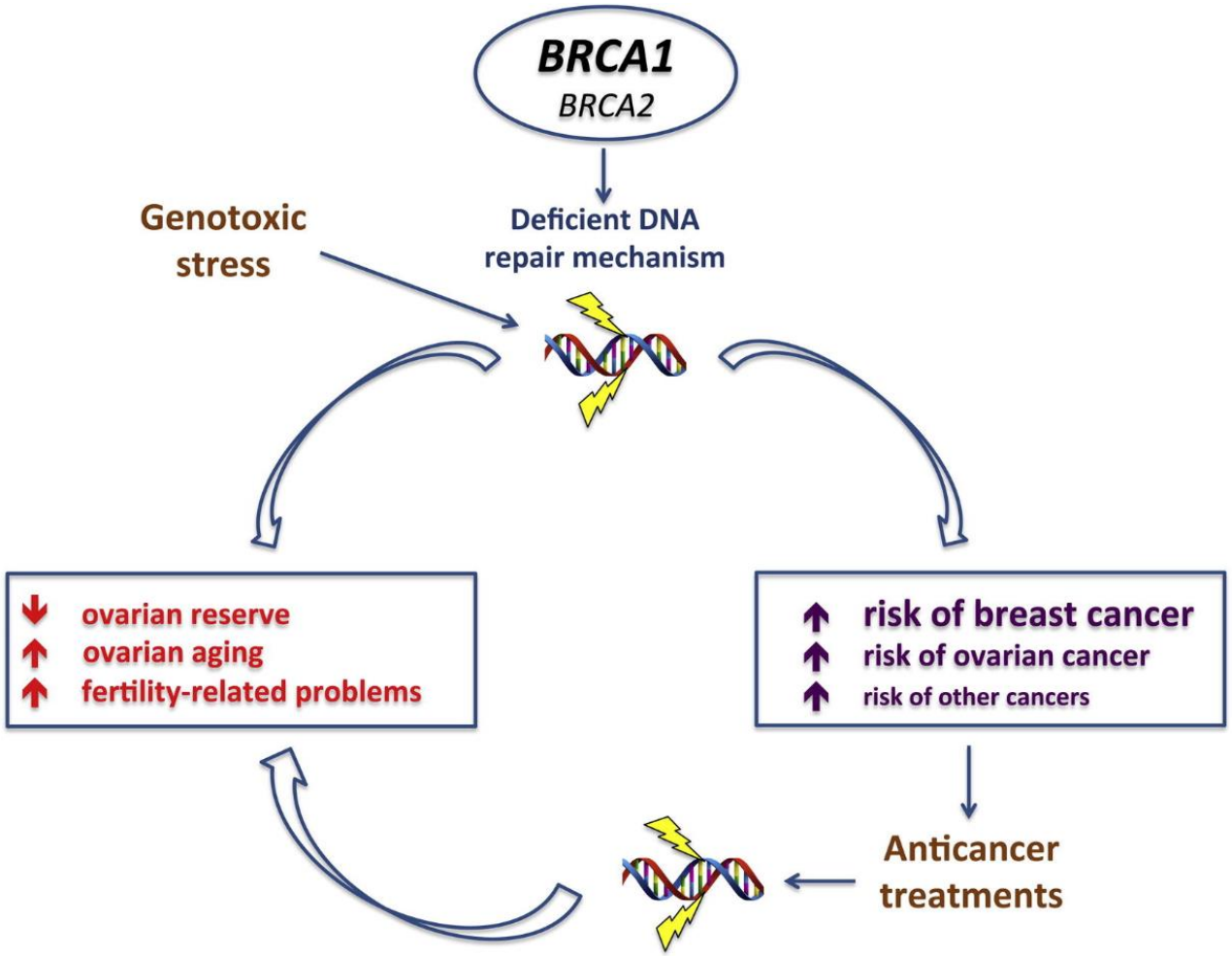
- Sperm cryopreservation and oocyte or embryo cryopreservation are the preferred options and should be proposed to newly diagnosed patients with hereditary cancer syndromes interested in fertility preservation [IV, A].
- Post-treatment pregnancies in *BRCA*-mutated breast cancer survivors should not be discouraged [IV, B]. Although no data are available for patients with pathogenic variants other than *BRCA*, there are no plausible reasons to anticipate different safety considerations for post-treatment pregnancies between cancer survivors with or without hereditary cancer syndromes [V, B].

Lambertini et al, 2020

Specific questions related to BRCA mutation and fertility

- Is pregnancy affect the oncological outcomes in breast cancer?
- **Is the BRCA mutation affect the ovarian reserve and fertility preservation performance?**
- Does ovarian stimulation safe in BRCA carriers?
- Does ART after breast cancer influence the prognosis in BC survivors?
- Does it impact the chemotherapy-induced ovarian damage? -new therapy?

Hypothesis



Lambertini M et al, Cancer Treat Rev 2017.

Impact on the ovarian reserve

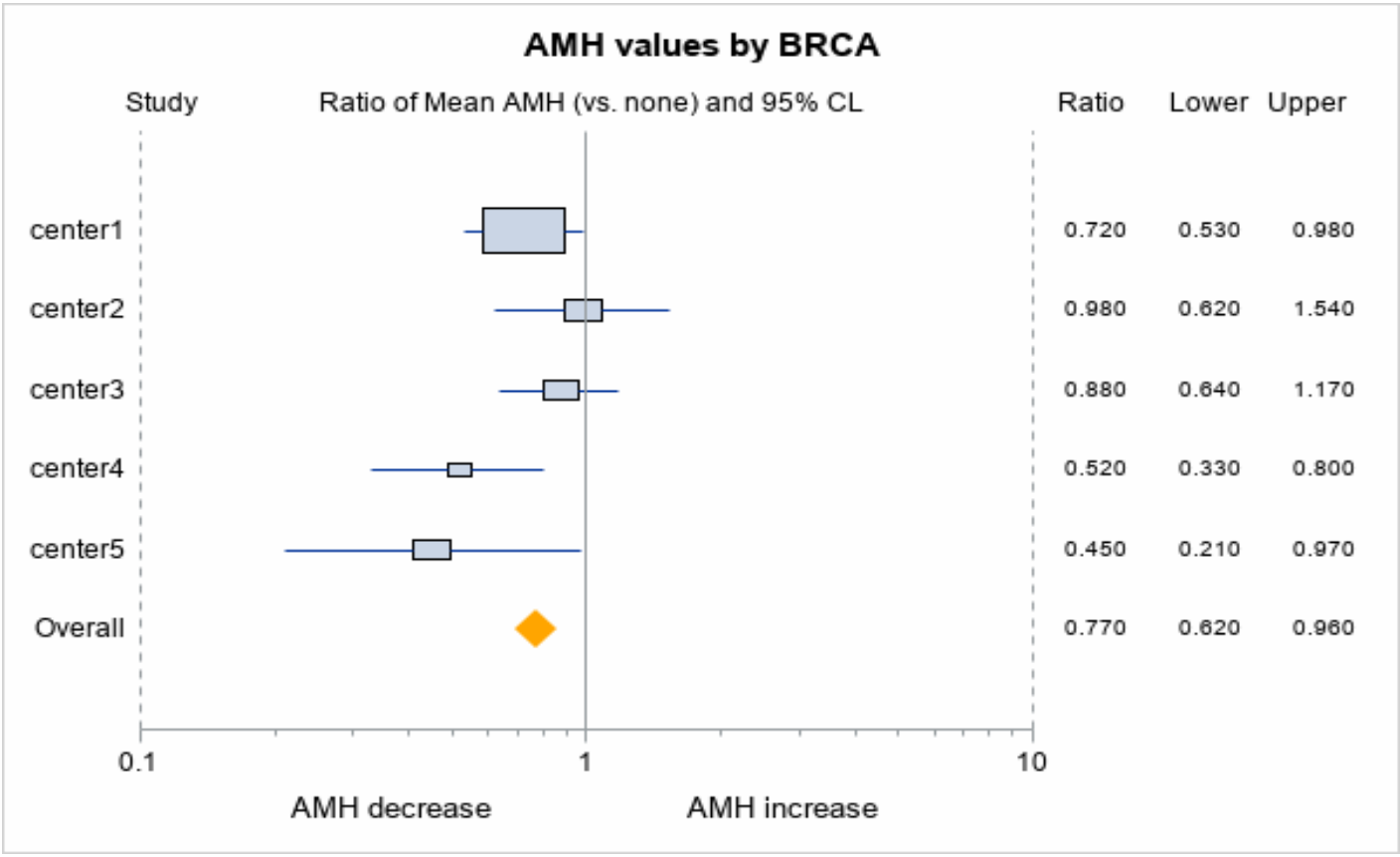
original reports

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, MD[5]; Erica Wang, MD[6]; Florian Clatot, MD[7]; Beth Y. Karlan, MD[8]; Isabelle Demeestere, MD[9]; Heejung Bang, PhD[10]; and Kutluk Oktay, MD, PhD[1,11]

250 BRCA carriers vs 578 control

Characteristic	g*BRCA*-Positive (N = 246)	g*BRCA*-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)
BRCA mutation type,[a] No. (%)		
g*BRCA1*	153 (62.2)	NA
g*BRCA2*	93 (37.8)	
Breast cancer, No. (%)		
Yes	157 (63.8)	524 (90.6)
No	89 (36.2)	54 (9.3)



Turan et al 2021, JCO

Impact on fertility preservation performance

Follicle density		
Pavone et al. (2014)	35 risk-reducing surgery of which 15 *BRCA*+, 35 control	*BRCA*+ vs control: lower number of follicles per slide (15.4 vs 23.3; P < 0.05)
Lin et al. (2017)	13 *BRCA1*+ patients, 5 *BRCA2*+ patients, 12 control patients	*BRCA*+ vs control: lower number of PFs per mm³ (11.2 ± 6.7 vs 44.18 ± 6.1; P = 0.0002) *BRCA1*+ and *BRCA2*+ vs control: P = 0.0001 and P = 0.0003
Lambertini et al. (2018)	19 *BRCA*+ patients, 53 control patients	*BRCA*+ vs control: lower number of oocytes per mm² (0.33 vs 0.78; P = 0.153)
Antral follicle count (AFC)		
Grynberg et al. (2019)	52 *BRCA*+ patients, 277 control patients	*BRCA*+ vs control: similar AFC (3.6 ± 2.9 vs 4.1 ± 3.6; P = 0.3)
Gunnala et al. (2019)	38 *BRCA*+ BC, 53 control BC and 19 *BRCA*+ cancer-free, 600 control cancer-free	BC – *BRCA*+ vs control: similar AFC (15.2 ± 5.0 vs 13.9 ± 6.3; P = 0.757) Cancer-free – *BRCA*+ vs control: higher AFC (16.3 ± 3.9 vs 12.2 ± 5.4; P = 0.025)
Drechsel et al. (2022)	30 *BRCA*+ patients, 122 control patients	*BRCA*+ vs control: similar AFC (15.0 [10.8-20.3] vs 14.5 [9.0-20.0]; P = 0.54)

BRCA+: BRCA-mutated patients; BC: breast cancer

Dias Nunes et al, 2024 IJMS; Lambertini et al 2018 ESMO Open

Table 1. Oocyte cryopreservation in the BRCA-positive and BRCA-negative cohorts

	***BRCA*-positive cohort (*N* = 10, 34.5%)**			***BRCA*-negative cohort (*N* = 19, 65.5%)**	***P* values[a] (*BRCA*-positive versus *BRCA*-negative)**
	***BRCA1*-positive (*N* = 5, 50.0%)**	***BRCA2*-positive (*N* = 5, 50.0%)**	***BRCA*-positive cohort (*N* = 10, 100%)**		
Total FSH dose (IU), median (IQR)	2775 (2700–2850)	2775 (1800–3000)	2775 (1800–3000)	2025 (1575–2425)	0.085
Type of stimulation, *N* (%)					
Follicular	3 (60.0)	3 (60.0)	6 (60.0)	11 (57.9)	1.000
Random	2 (40.0)	2 (40.0)	4 (40.0)	8 (42.1)	
Stimulation days, median (IQR)	11 (10–11)	12 (12–12)	11.5 (10–12)	9 (8–11)	0.110
E2 at trigger (pmol/l), median (IQR)	419 (95–442)	187 (159–238)	213 (95–442)	200 (92–615)	0.909
P at trigger (pmol/l), median (IQR)	1.37 (0.81–1.76)	0.45 (0.45–1.50)	1.09 (0.45–1.76)	0.84 (0.59–1.40)	0.854
Number of oocytes, median (IQR)	7 (3–7)	6 (3–7)	6.5 (3–7)	9 (5–13)	0.145
Number of mature oocytes, median (IQR)	7 (3–7)	4 (2–5)	4.5 (2–7)	7 (5–9)	0.299
Maturation rate, median (IQR)	1.0 (1.0–1.0)	0.7 (0.7–0.7)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.888
Number of cryopreserved oocytes, median (IQR)	5 (2–7)	3 (2–4)	3.5 (2–7)	6 (4–12)	0.121
Poor response rate, *N* (%)	2 (40.0)	2 (40.0)	4 (40.0)	2 (11.1)	0.147

Ovarian stimulation

↑ FSH cumulative doses
↑ number of day
↓ oocytes yield and frozen
↑ Poor responder rate

Ovarian tissue cryopreservation

↓ Low follicular density

Impact on fertility preservation performance

Article

Response to Ovarian Stimulation for Urgent Fertility Preservation before Gonadotoxic Treatment in *BRCA*-Pathogenic-Variant-Positive Breast Cancer Patients

Lina El Moujahed [1], Robin Philis [2], Michael Grynberg [1,2], Lucie Laot [1], Pauline Mur [1], Noemi Amsellem [1], Anne Mayeur [3], Alexandra Benoit [1], Sophia Rakrouki [2], Christophe Sifer [4], Maeliss Peigné [2] and Charlotte Sonigo [1,5,6,*]

	BRCA (*n* = 57)	Non-*BRCA* (*n* = 254)	*p*
Females' characteristics			
Age (years) [a]	33.4 (30.5–36)	33.2 (30.5–36.2)	0.77
AFC (follicles)	16 (12–25)	19 (12–27)	0.35
AMH (ng/mL) [a]	1.6 (0.8–2.9)	2.4 (1.4–3.7)	0.02
Total dose of gonadotropins (IU) [a]	2700 (2400–3937)	3000 (2062–3600)	0.73
No of retrieved oocytes [a]	10 (6–15)	11 (7–17)	0.16
No of metaphase II oocytes [a]	7 (4.5–11.5)	9 (5–14)	0.05
Oocyte retrieval rate (%)	63.6 (40.0–80.1)	58.8 (38.5–83.3)	0.95
Oocyte maturation rate (%)	78.6 (53.1–96.4)	85.7 (70–100)	0.04

Article

Impact of Breast Cancer and Germline BRCA Pathogenic Variants on Fertility Preservation in Young Women

Elze Prokurotaite [1,*], Margherita Condorelli [1,2], Julie Dechene [2], Jason Bouziotis [3], Matteo Lambertini [4,5] and Isabelle Demeestere [1,2]

	Group 1 BC Patients without a gBRCA PV n = 55 (64.7%)	Group 2 BC Patients with a gBRCA PV n = 20 (23.5%)	Group 3 Healthy gBRCA PV Carriers n = 10 (11.8%)	*p* Value
Baseline hormone level—median [range]				
AMH (µg/L)	2.3 [0.3–13]	1.7 [0.2–4.7]	1.8 [0.5–8.3]	0.22
FSH (IU/L)	5 [1–21]	6.2 [3–15]	5.5 [1–9.7]	0.15
E2 (ng/L)	42 [12–499]	25 [16.5–135]	43 [16–289]	0.09
OS outcomes				
Number of oocytes collected—median [range]	8 [0–21]	6 [1–22]	8 [1–29]	0.36
Number of oocytes collected—mean ± SD	8.9 ± 5,2	7.7 ± 6.2	9.3 ± 6.9	
Number of mature oocytes collected—median [range]	6 [0–18]	5 [1–21]	6 [1–26]	0.41
Number of mature oocytes collected—mean ± SD	7.2 ± 4.5	6.9 ± 6.1	8 ± 6.2	
Maturation rate (%)—mean ± SD	81.0 ± 20.7	86.2 ± 19.9	89.4 ± 17.1	0.26

Impact on the succes of the procedure???

Specific questions related to BRCA mutation and fertility

- Is pregnancy affect the oncological outcomes in breast cancer?
- Is the BRCA mutation affect the ovarian reserve and fertility preservation performance?
- **Does ovarian stimulation safe in BRCA carriers?**
- **Does ART after breast cancer influence the prognosis in BC survivors?**
- Does it impact the chemotherapy-induced ovarian damage? -new therapy?

Fertility preservation is recommended in BC carriers!

PGT-M

Risk of breast cancer

CARE DELIVERY

editorials

Fertility Considerations for Reproductive-Aged Carriers of Deleterious BRCA Mutations: A Call for Early Intervention

Eliana Fine, MD[1,2]; Miriam A. Knoll, MD[1,3]; and Bat-Sheva L. Maslow, MD, MSCTR[1,4]

ASCO

JCO® Oncology Practice

Risk-reducing Surgery

Impact on ovarian reserve

Safe

Fine et al, 2021, Huber et al, 2020

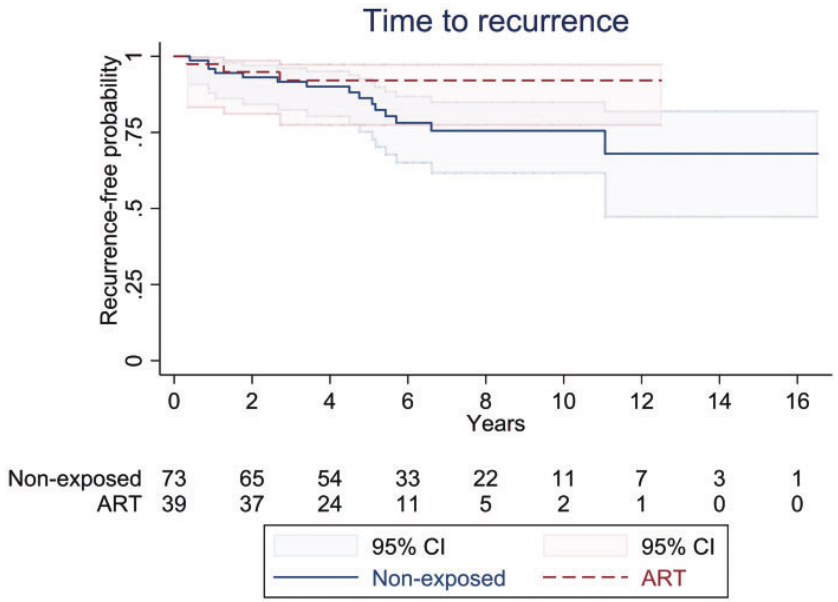
ART after breast cancer

Human Reproduction, pp. 1–9, 2020
doi:10.1093/humrep/deaa319

human reproduction ORIGINAL ARTICLE *Infertility*

Impact of ARTs on oncological outcomes in young breast cancer survivors

M. Condorelli[1,2,*], M. De Vos[3], S. Lie Fong[4], C. Autin[5], A. Delvigne[6], F. Vanden Meerschaut[7], C. Wyns[8], R. Imbert[9], C. Cheruy[10], J. Bouziotis[11], E. de Azambuja[12], A. Delbaere[1], M. Lambertini[2,13,14], and I. Demeestere[1,2]



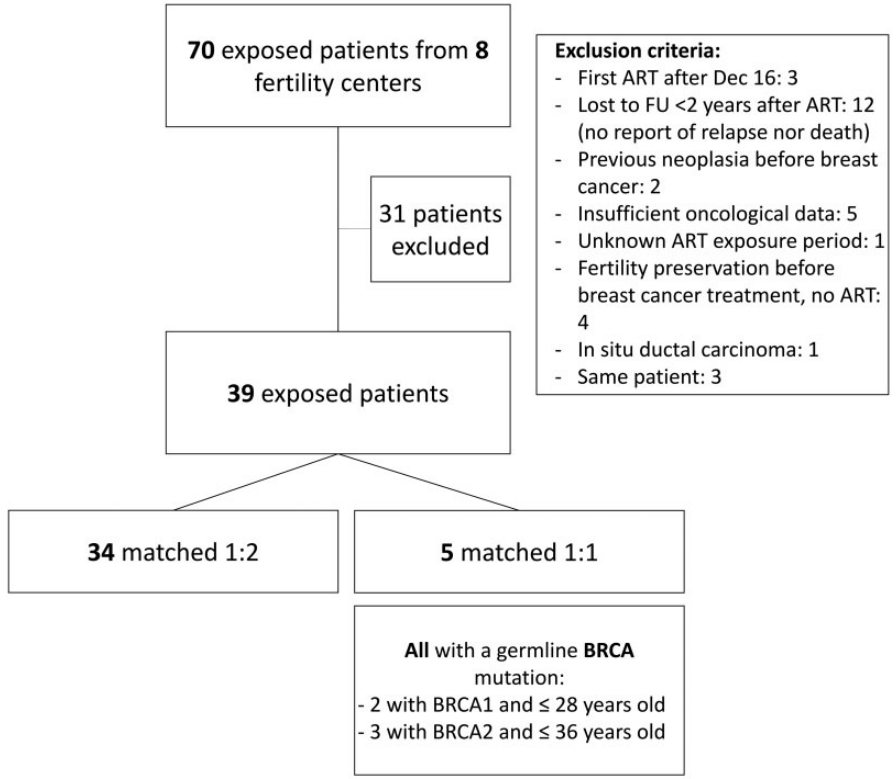


Table V Main oncologic and ART data of exposed patients that experienced a relapse.

Patient	Stage		Hormonal receptors	FSH (IU/l)	AMH (ng/ml)	ART	E2 (pg/ml)	Pregnancy and delivery	Interval between the start of ART and relapse/pregnancy and relapse (years)	Interval between the first breast cancer and the relapse (years)
	T	N								
Patient 1	2	0	Positive	200	<0.1	4 FET in HRT	1347.2	No	1	7
Patient 2	1	0	Positive	66.9	0.1	1 FET in HRT	139.7	One pregnancy and a livebirth	2/2	9
Patient 3	1	0	Positive	17.3	<0.1	2 ovarian stimulations for IVF/ICSI	1700	No	A few months after starting ART	4

AMH, anti-Müllerian hormone; E2, serum oestradiol peak during ART; FET, frozen embryo transfer; HRT, hormone replacement therapy.

ART in breast cancer patients

- *BRCA* BCY Collaboration (NCT03673306)

Table 3. Oncological outcomes

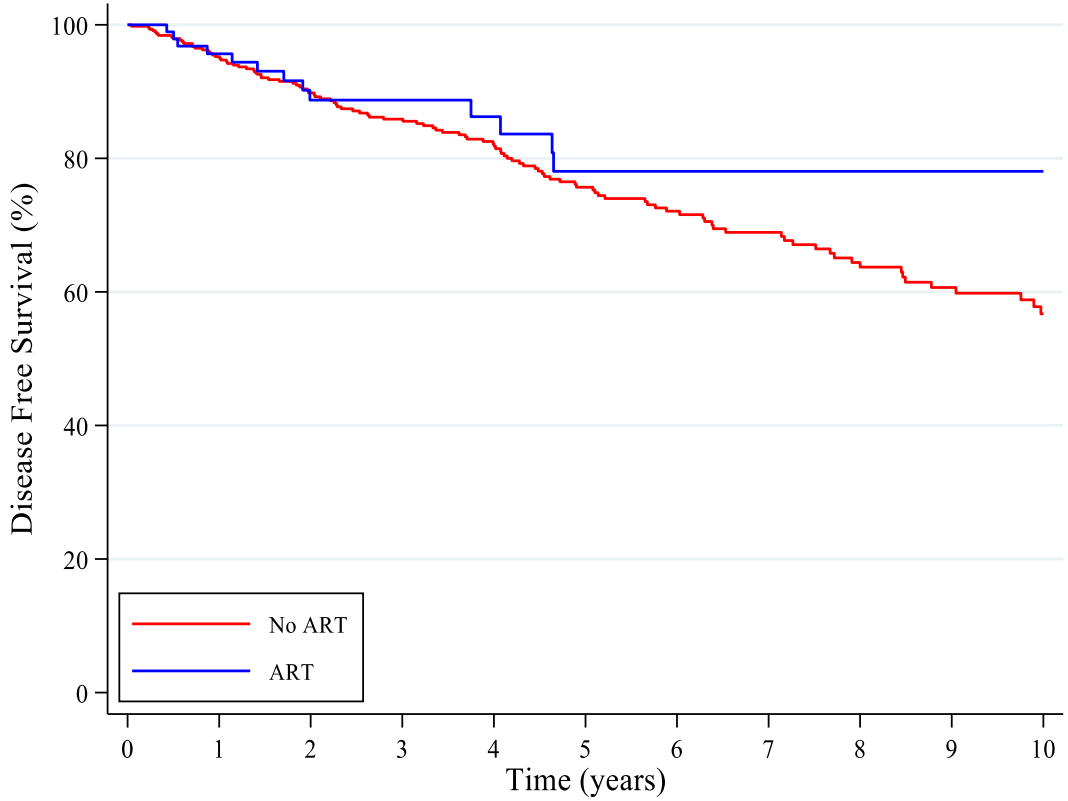
	ART group (n = 22)	Non-ART group (n = 146)
DFS event, *n* (%)		
No	20 (90.9)	106 (72.6)
Yes	2 (9.1)	40 (27.4)
DFS type, *n* (%)		
Locoregional recurrence of primary invasive breast cancer	2 (9.1)	7 (4.8)
Distant recurrence (with or without locoregional recurrence) of primary invasive breast cancer	0 (—)	10 (6.9)
Second primary breast cancer	0 (—)	19 (13.0)
Second primary malignancy	0 (—)	4 (2.7)
Death without recurrence	0 (—)	0 (—)
Death, *n* (%)		
No	22 (100.0)	136 (93.1)
Yes	0 (—)	10 (6.9)
Median follow-up from breast cancer diagnosis, years (IQR)	7.5 (6.5-10.5)	8.8 (6.8-11.8)
Median time from breast cancer diagnosis to DFS event, years (IQR)	7.5 (6.5-10.5)	7.9 (5.6-10.5)
Median follow-up from conception, years (IQR)	3.4 (1.1-5.5)	5.0 (2.8-7.7)
Median time from conception to DFS event, years (IQR)	3.4 (1.1-5.3)	3.7 (2.0-6.1)

ART, assisted reproductive techniques; DFS, disease-free survival; IQR, interquartile range.

Condorelli et al, ESMO Open 2021

N=1252 patients in 30 centers

Updated *BRCA* BCY Collaboration



Number at risk

No ART	436	374	308	269	230	181	145	114	93	73	53
ART	99	78	60	42	34	27	21	20	14	11	8

	Patients in the ART group n = 99, N (%)	Patients in the no-ART group n = 436, N (%)
Number of DFS events	13 (13.1)	118 (27.1)
Log-rank p=0.147		

Lambertini et al, JAMA 2024

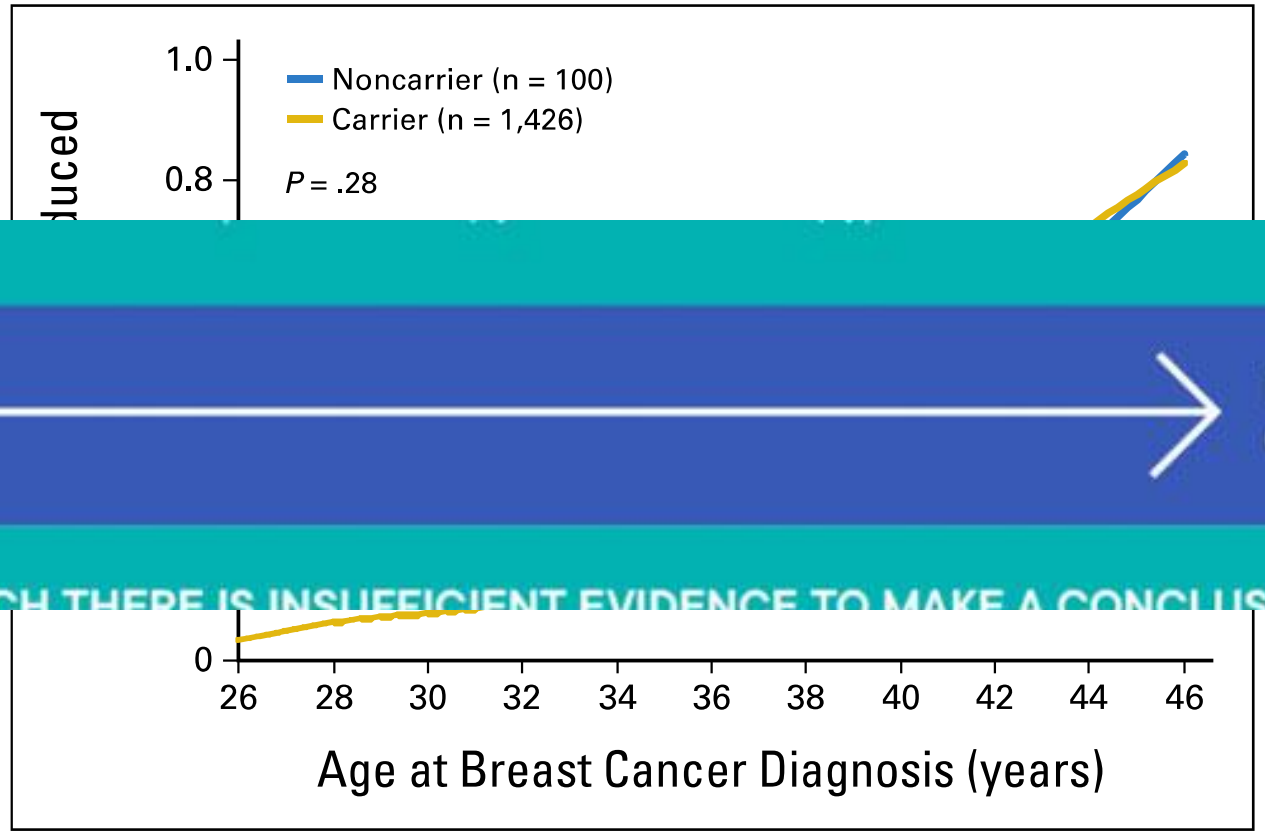
>4000 patients in 78 centers

Specific questions related to BRCA mutation and fertility

- Is pregnancy affect the oncological outcomes in breast cancer?
- Is the BRCA mutation affect the ovarian reserve and fertility preservation performance?
- Does ovarian stimulation safe in BRCA carriers?
- Does ART after breast cancer influence the prognosis in BC survivors?
- **Does it impact the chemotherapy-induced ovarian damage? -new therapy?**

Chemotherapy-induced amenorrhea

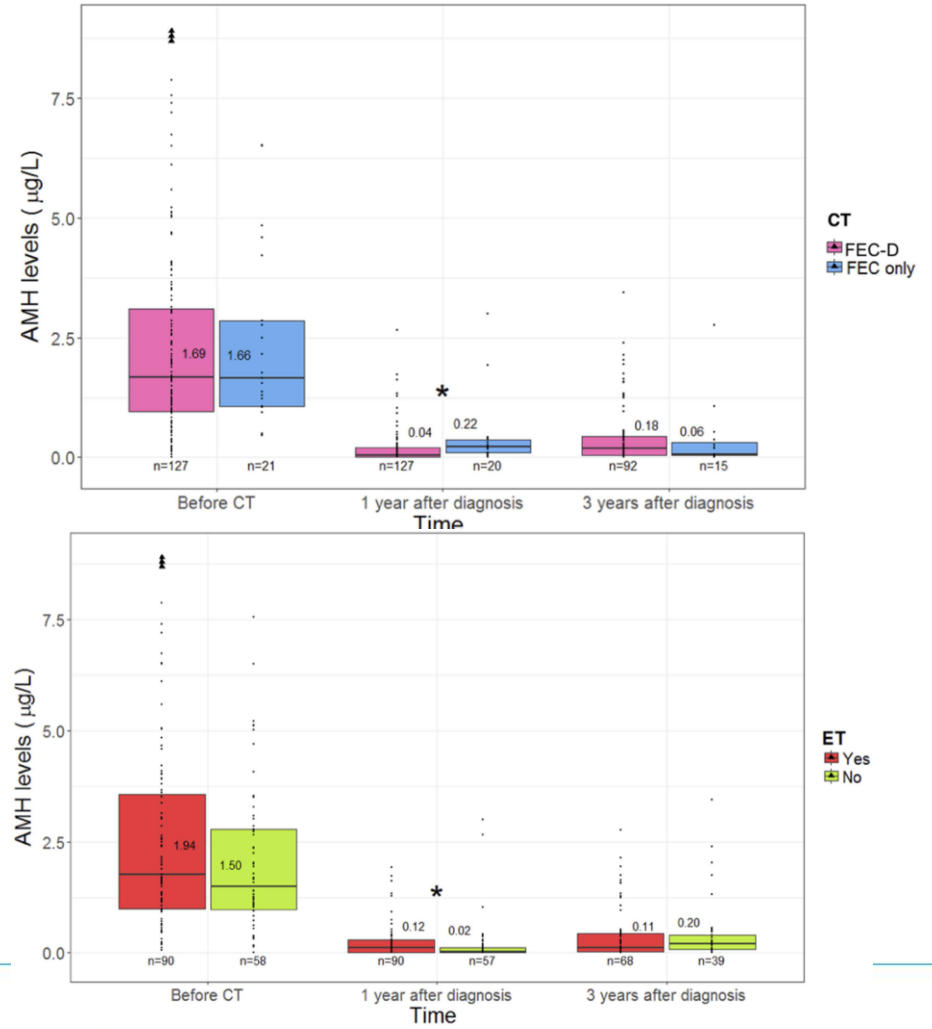
No apparent increased risk of gonadotoxicity in *BRCA*-mutated patients

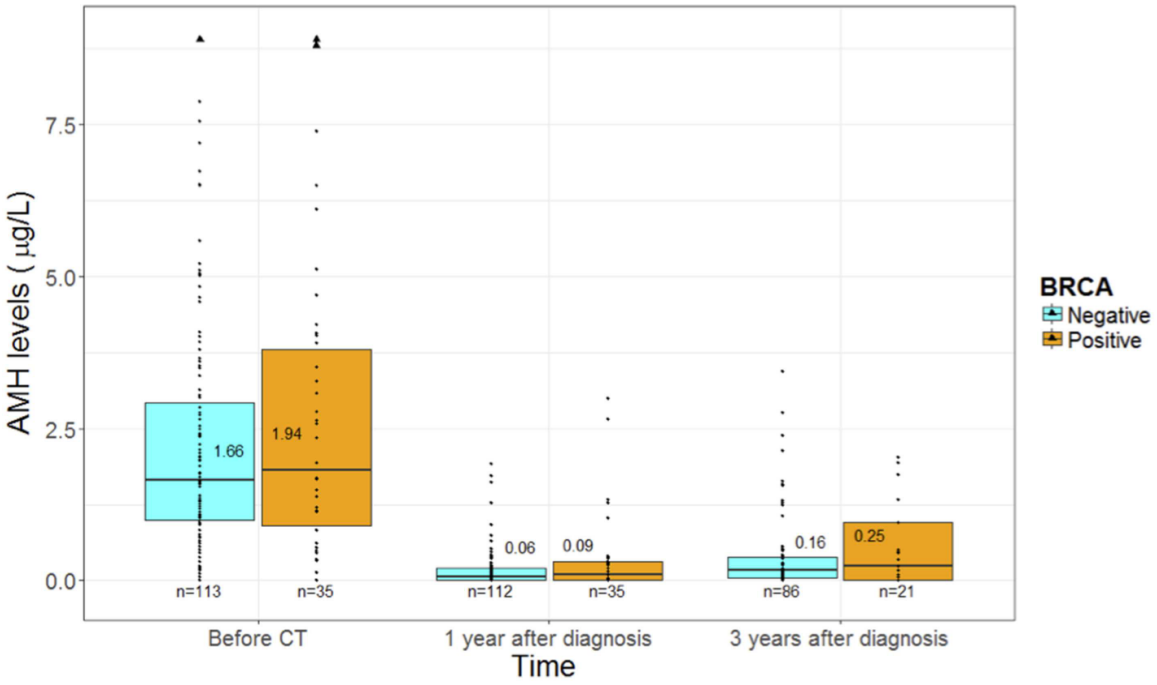


Valentini A et al, J Clin Oncol 2013

Impact of the treatment on ovarian reserve

Impact of adding taxanes (D), endocrine therapy (ET) in breast cancer patients

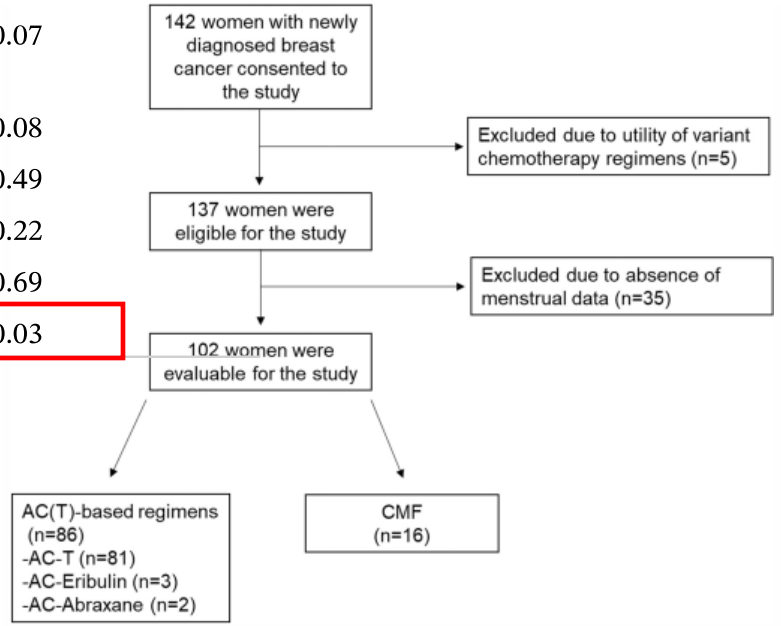




Lambertini et al, 2019

BRCA as a negative factor?

Predictors	Unadjusted model odds ratio (95% CI), *p*-value	Adjusted model odds ratio (95% CI), *p*-value AUC = 0.76
(c) Outcome = amenorrhea at 18 months		
AMH at baseline ($n = 102$) (per 0.1 increase)	0.97 (0.94, 0.99), $p = 0.01$	0.98 (0.95, 1.00), $p = 0.07$
Age (per 1 year) ($n = 102$)	1.12 (1.02, 1.24), $p = 0.02$	1.12 (0.99, 1.27), $p = 0.08$
BMI (per 1 unit) ($n = 102$)	1.03 (0.94, 1.12), $p = 0.54$	1.04 (0.93, 1.16), $p = 0.49$
Tamoxifen ($n = 81$)	2.42 (0.64, 9.17), $p = 0.19$	2.64 (0.56, 12.3), $p = 0.22$
AC-based regimen ($n = 86$)	0.70 (0.23, 2.15), $p = 0.53$	1.31 (0.34, 5.01), $p = 0.69$
gBRCApv-positive ($n = 12$)	3.10 (0.87, 11.1), $p = 0.08$	5.59 (1.21, 25.8), $p = 0.03$



Oktay et al, 2023

Personalized therapy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

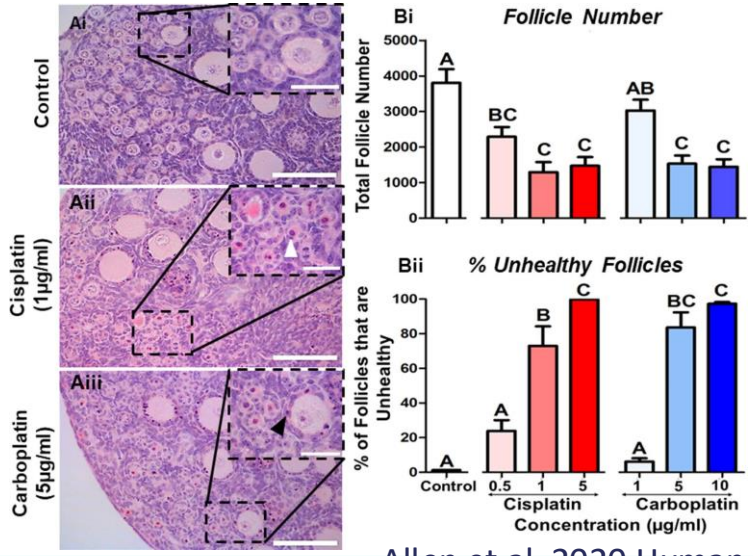
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4)

S. Paluch-Shimon[1*†], F. Cardoso[2†], A. H. Partridge[11†], O. Abulkhair[3], H. A. Azim Jr[4], G. Bianchi-Micheli[5], M.-J. Cardoso[2,20], G. Curigliano[6,7], K. A. Gelmon[8], N. Harbeck[9], J. Merschdorf[10], P. Poortmans[12], G. Pruneri[13], E. Senkus[14], T. Spanic[15], V. Stearns[16], Y. Wengström[17], F. Peccatori[18‡] & O. Pagani[19‡]

Guidelines	LoE, GoR	Consensus
In patients with TNBC or *BRCA*-associated tumours the incorporation of platinum agents increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated.	[I, B]	



Allen et al, 2020 Human reprod

High risk	Intermediate risk	Low/no risk
Cyclophosphamide	Doxorubicin	Methotrexate
Busulfan	Cisplatin	Bleomycin
Melphalan	Carboplatin	5-Fluorouracil
Chlorambucil		Actinomycin-D
Dacarbazine		Mercaptopurine
Procarbazine		Vincristine
Ifosfamide		
Thiotepa		
Nitrogen mustard		

Combination with Paclitaxel

Animal model

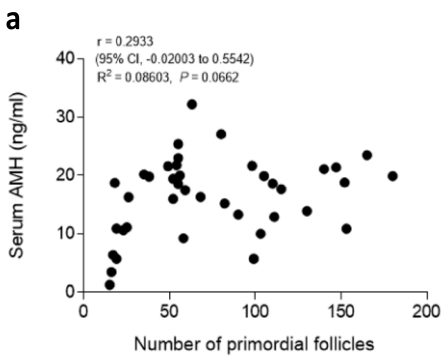
OPEN

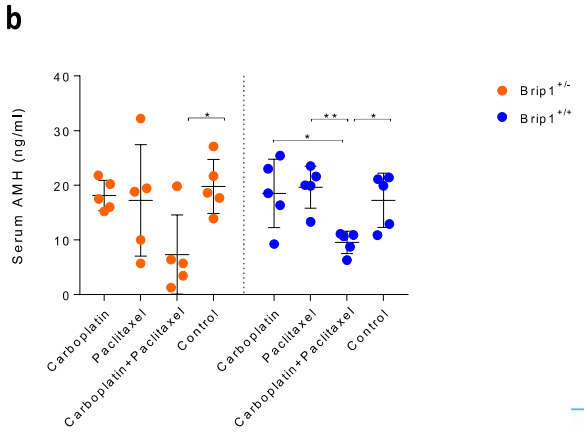
Ovarian toxicity of carboplatin and paclitaxel in mouse carriers of mutation in *BRIP1* tumor suppressor gene

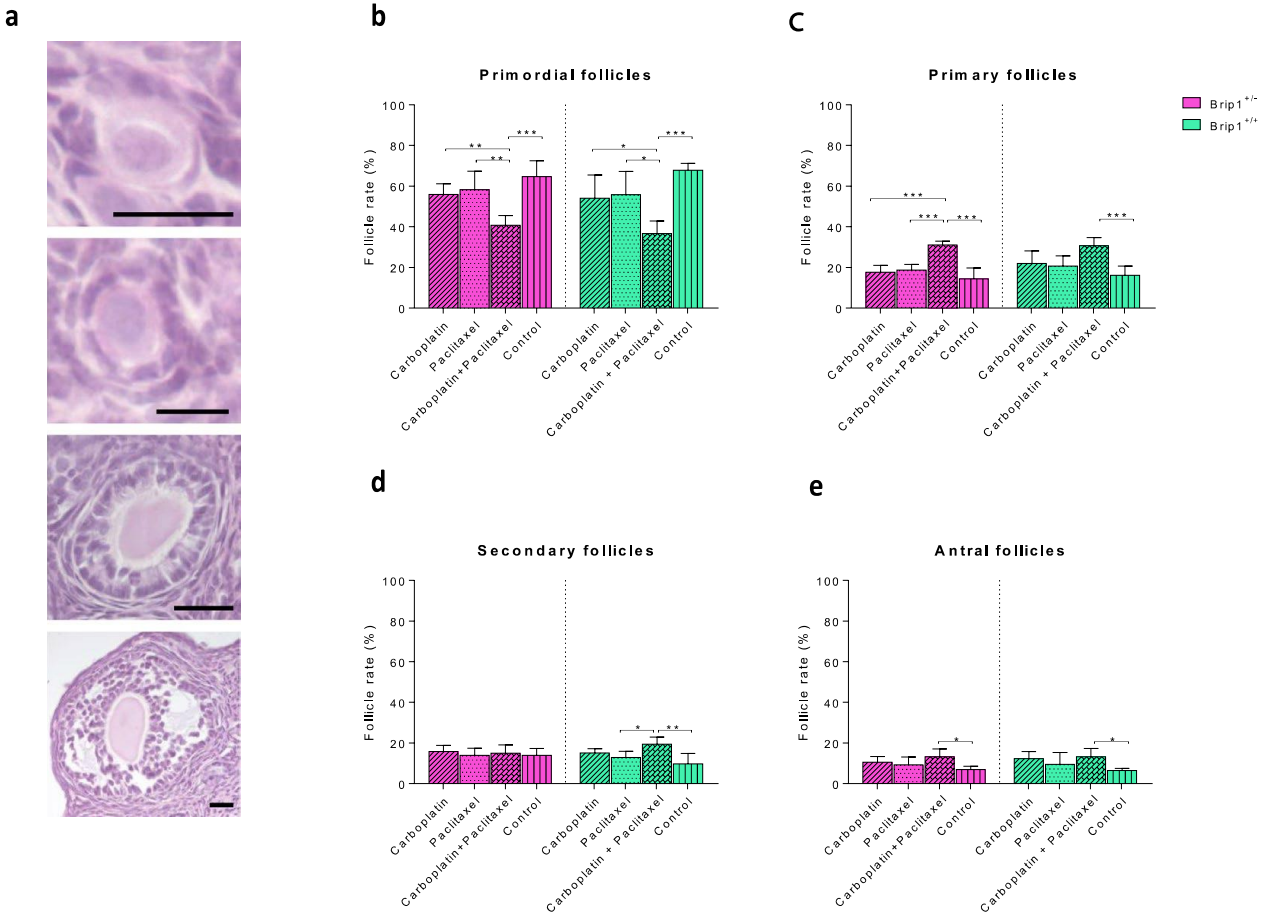
E. Ntemou[1], P. Diaz Vidal[1], C. Alexandri[1], G. Van den Steen[1], M. Lambertini[2,3] & I. Demeestere[1,4]✉

Mouse model:

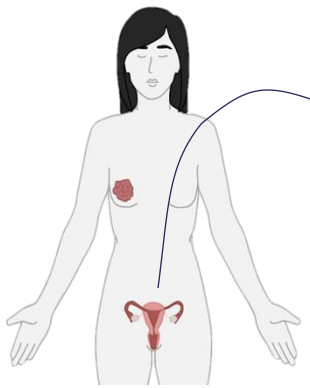
- Brip1$^{em1(IMPC)J}$
- intervention in HR process mediated by BRCA1







Human model



Ovarian tissue cryopreservation

OTT

Residual tissue donated to research

- Breast cancer patients
- ≤ 35 years

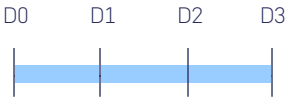
In vitro model

Thawed ovarian tissue

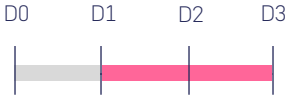
3 days *in vitro* culture

1 Control

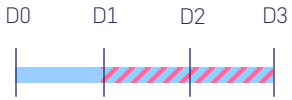
2 Carboplatin 10µg/mL



3 Paclitaxel 1µM



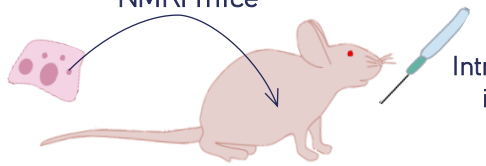
4 Carboplatin 10µg/mL + paclitaxel 1µM



In vivo model

Thawed ovarian tissue

Xenotransplantation into the peritoneum of NMRI mice

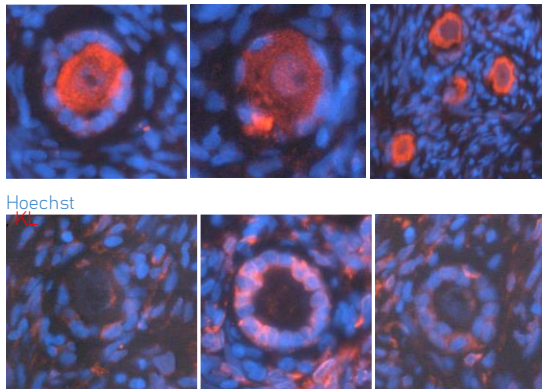


Intraperitoneal injections

1 Control

2 Carboplatin 50 mg/kg and paclitaxel 10 mg/kg

Carboplatin and Paclitaxel



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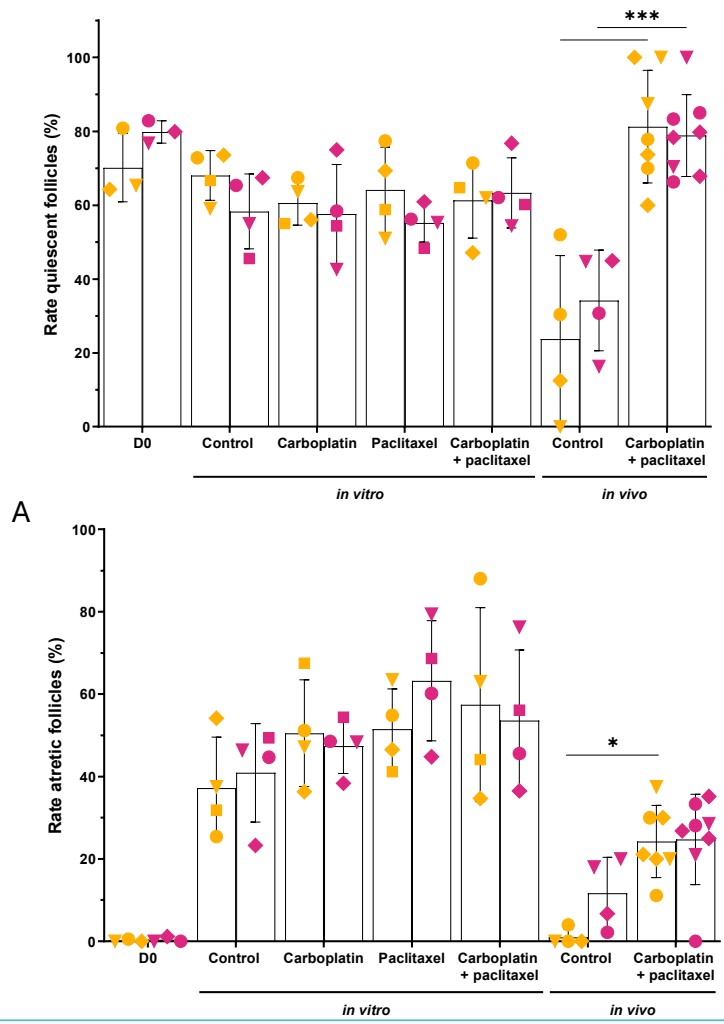
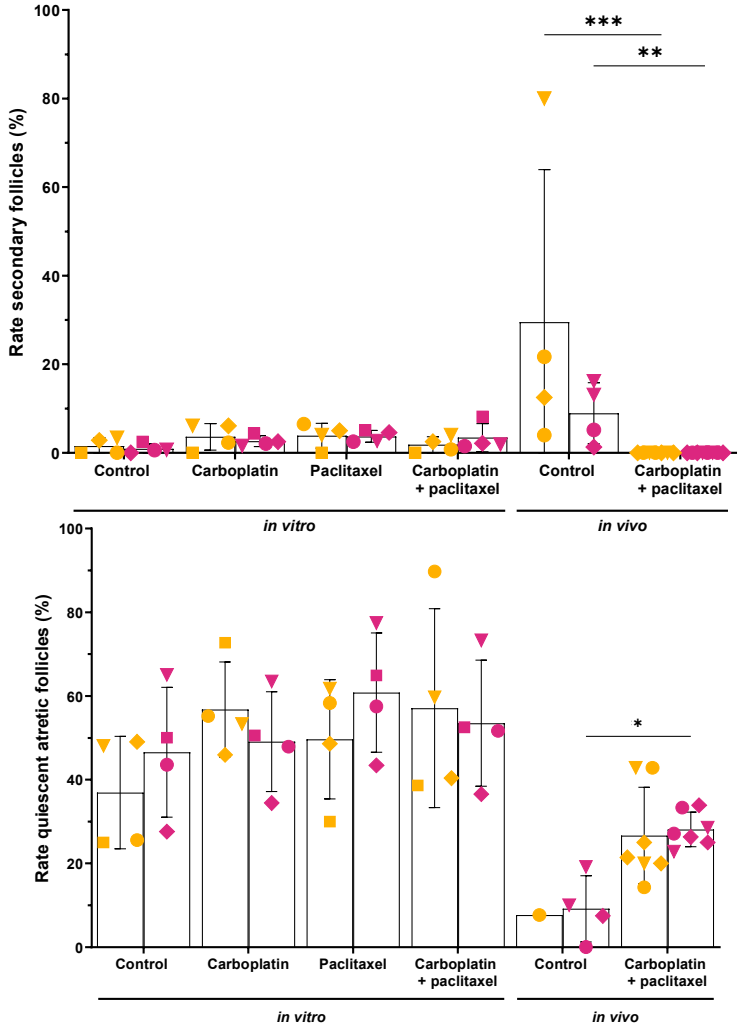
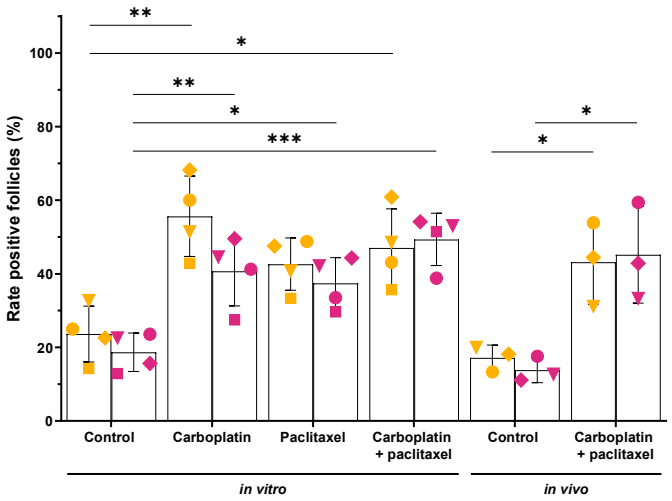
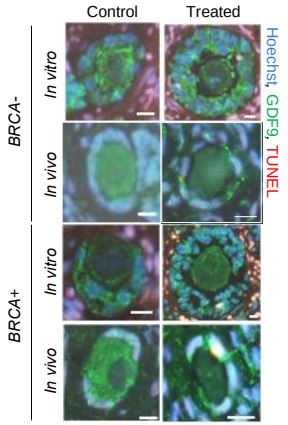
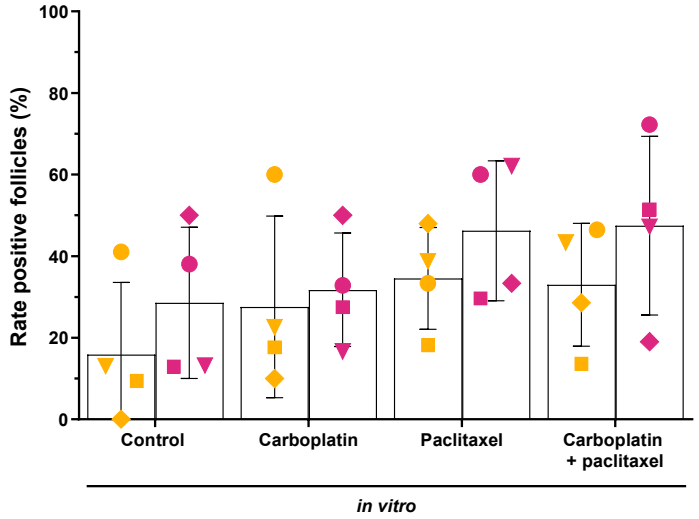


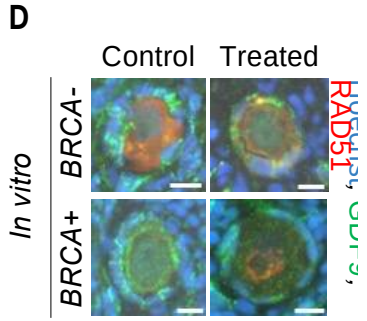


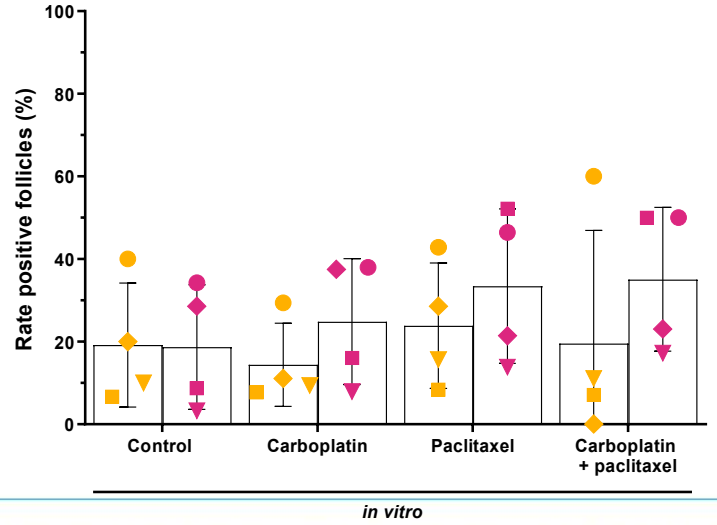
Apoptosis and DDR

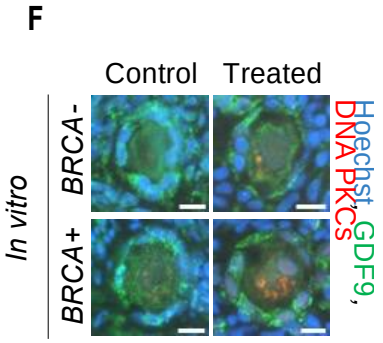












Impact of age?

Impact on stroma?

Conclusion

- Pregnancy and ART do not impact oncological outcomes of BRCA1 mutation carriers and BC survivors.
- BRCA mutation carriers (BRCA1) have a lower ovarian reserve but it does not impact the chance of spontaneous pregnancy.
- Breast cancer patients harbouring BRCA1 mutation have a lower fertility preservation and IVF procedures performance.
- No evidence of increase treatment-related POI in BRCA patients but impact remains unclear
- Several research priorities remains in this field (new drug regimen, oocytes quality, impact of the age, pregnancy outcomes of fertility preservation, effect of other mutation on genes such as PALB2, PTEN, ATM …)

Thank you!

Research Lab on Human Reproduction

Fertility Clinic HUH-Erasme

Collaborator:
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IRCCS Ospedale Policlinico San Martino – University of Genova (Italy)