Carcinoma Mammario: I Traguardi Raggiunti e le Nuove Sfide
Il Carcinoma Mammario nelle Donne con Mutazione Patogenetica BRCA1-BRCA2

La Gravidanza dopo Carcinoma Mammario in Donne con Mutazione BRCA

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Gruppo Italiano Mammella GIM

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ESMO

Disclosure Information

Relationship Relevant to this Session

Lambertini, Matteo:

- **Consultant or advisor:** Teva
- **Honoraria:** Theramex, Takeda

Outline

- **Introduction**
- **Fertility preservation in breast cancer patients with *BRCA* mutations**
- **Safety of pregnancy after breast cancer in patients with *BRCA* mutations**
- **Conclusions**

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- Conclusions

Fertility and Pregnancy Concerns in Young Breast Cancer Patients – Who Cares?

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

BCY4

Fertility and Pregnancy Concerns in *BRCA*-Mutated Breast Cancer Patients

1

Genetic Inheritance

The Oncologist®

Breast Cancer, BRCA Mutations, and Attitudes Regarding Pregnancy and Preimplantation Genetic Diagnosis

Ashley H. Woodson, Kimberly I. Muse, Heather Lin, Michelle Jackson, Danielle N. Mattair, Leslie Schover, Terri Woodard, Laurie McKenzie, Richard L. Theriault, Gabriel N. Hortobágyi, Banu Arun, Susan K. Peterson, Jessica Profato, Jennifer K. Litton

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Open

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

***BRCA1/2* carriers: their childbearing plans and theoretical intentions about having preimplantation genetic diagnosis and prenatal diagnosis**

Claire Julian-Reynier, MD, MSc[1–4], Roxane Fabre, MSc[1–3], Isabelle Coupier, MD, PhD[5], Dominique Stoppa-Lyonnet, MD, PhD[6,7], Christine Lasset, MD, PhD[8,9], Olivier Caron, MD[10], Emmanuelle Mouret-Fourme, MD[6,11], Pascaline Berthet, MD[12], Laurence Faivre, MD[13,14], Marc Frenay, MD[15], Paul Gesta, MD[16], Laurence Gladieff, MD[17], Anne-Deborah Bouhnik, PhD[1–3], Christel Protière, PhD[1–3] and Catherine Noguès, MD[6,11]

2

Prophylactic Surgery

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v103–v110, 2016
doi:10.1093/annonc/mdw327

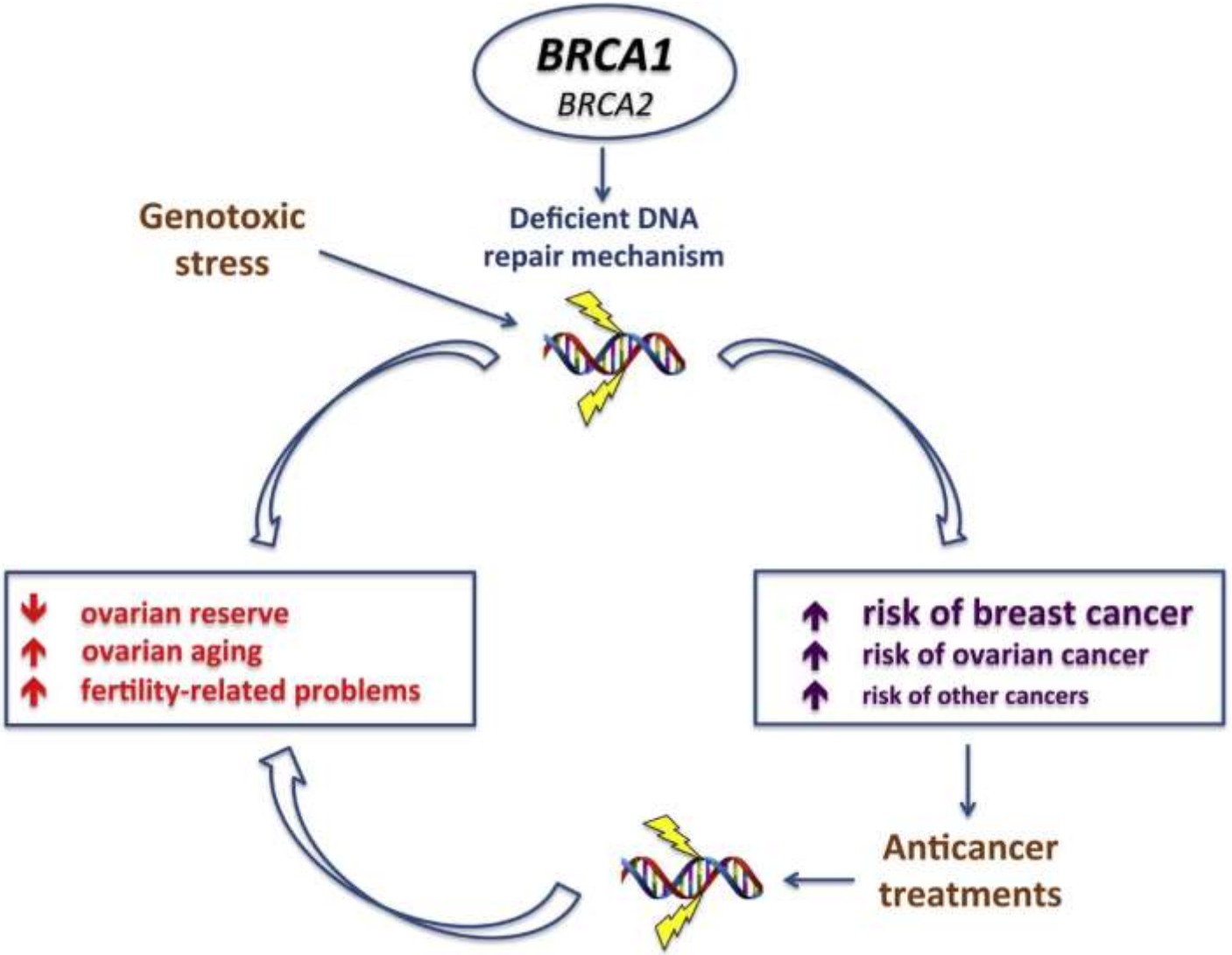
Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

S. Paluch-Shimon[1], F. Cardoso[2], C. Sessa[3], J. Balmana[4], M. J. Cardoso[2], F. Gilbert[5] & E. Senkus[6], on behalf of the ESMO Guidelines Committee*

Woodson AH et al, The Oncologist 2014;19:797-804. Julian-Reynier C et al, Genet Med 2012;14(5):527-34
Paluch-Shimon S et al, Ann Oncol 2016;27(Suppl 5):v103-v110

Fertility and Pregnancy Concerns in *BRCA*-Mutated Breast Cancer Patients

3



Lambertini M et al, Cancer Treat Rev 2017; 59:61-70

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Risk of Treatment-Related Premature Ovarian Insufficiency (POI) in Breast Cancer Patients

Degree of risk	Type of anticancer treatment
High risk (> 80%)	CMF, CEF, CAF, TAC × 6 cycles in women ≥ 40 years
Intermediate risk (40–60%)	CMF, CEF, CAF, TAC × 6 cycles in women of 30–39 years -AC × 4 cycles in women ≥ 40 years -FEC × 6 cycles -ddFEC × 6 cycles -AC × 4 cycles → T × 4 cycles -EC or FEC × 4 cycles → P × 4 cycles -ddEC or ddFEC × 4 cycles → ddP × 4 cycles
Low risk (< 20%)	CMF, CEF, CAF, TAC × 6 cycles in women ≤ 30 years -AC × 4 cycles in women ≤ 40 years
Very low or no risk	Methotreaxte -Fluorouracil -Tamoxifen -Trastuzumab (?)
Unknown risk	Targeted agents: pertuzumab, lapatinib, T-DM1, bevacizumab, everolimus, CDK4/6 inhibitors, PARP inhibitors

Lambertini M et al, Curr Opin Oncol 2017;29(4):243-52

Oncofertility Counseling is Mandatory As soon as Possible after Diagnosis

clinical practice guidelines

Annals of Oncology 00: 1–11, 2013
doi:10.1093/annonc/mdt199

Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. A. Peccatori[1], H. A. Azim Jr[2], R. Orecchia[3], H. J. Hoekstra[4], N. Pavlidis[5], V. Kesic[6] & G. Pentheroudakis[5], on behalf of the ESMO Guidelines Working Group*

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Aiom
Associazione Italiana di Oncologia Medica

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

Linee guida

Peccatori F et al, Ann Oncol 2013;24:vi160-70
Lambertini M et al, Eur J Cancer 2017;71:25-33. Oktay K et al, J Clin Oncol 2018;36(19):1994-2001

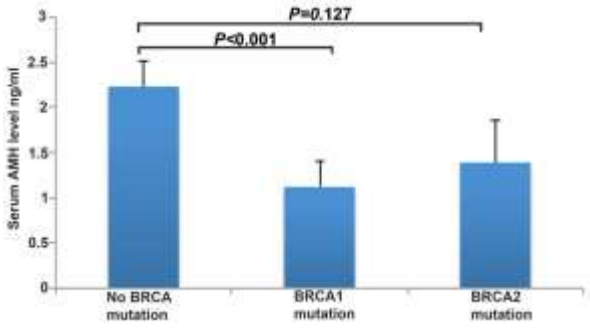
Oncofertility Counseling is Mandatory As soon as Possible after Diagnosis Including in Patients with Advanced Disease

Guideline statement	LoE/GoR	Consensus
Fertility preservation: the impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).	Expert opinion/ B	100%

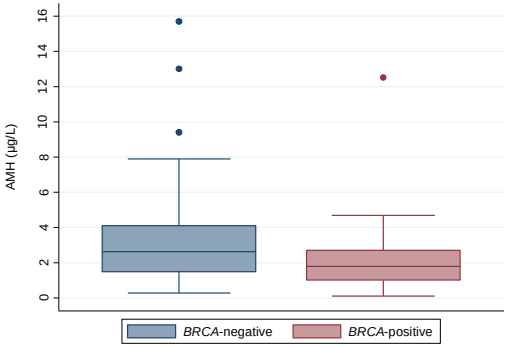
Cardoso F et al, Ann Oncol 2018;29(8):1634-57

Reproductive Potential – Ovarian Reserve in *BRCA*-Mutated Breast Cancer Patients

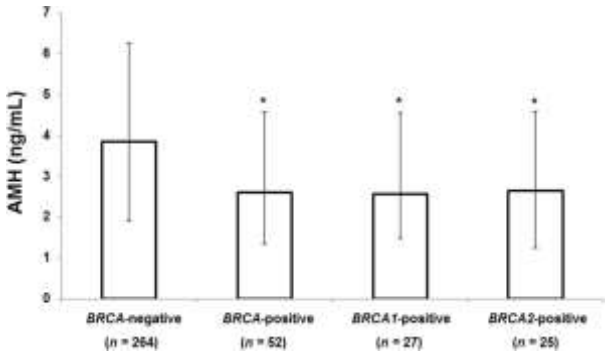
***BRCA*-mutated breast cancer patients appear to have a lower ovarian reserve (AMH levels) as compared to noncarriers**



n=60 n=24



	BRCA-negative cohort (n=60)	*BRCA*-positive cohort (n=25)	P values
Anti-Müllerian hormone levels, median (IQR)	2.6 (1.5-4.1)	1.8 (1-2.7)	0.109
Anti-Müllerian hormone levels, N (%)			
≤ 1.0	12 (20.0)	8 (32.0)	0.235
> 1.0	48 (80.0)	17 (68.0)	



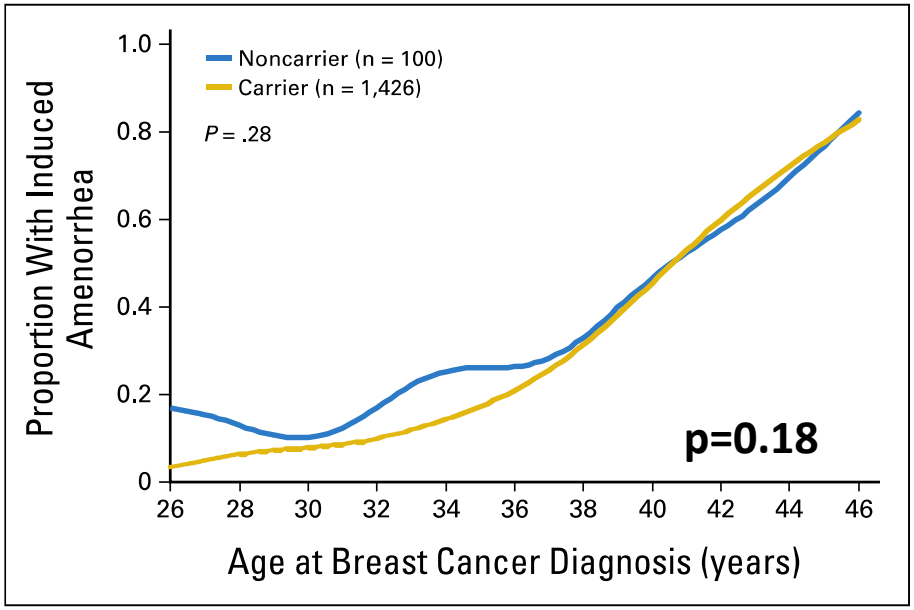
*$P < 0.05$ vs. *BRCA*-negative patients.

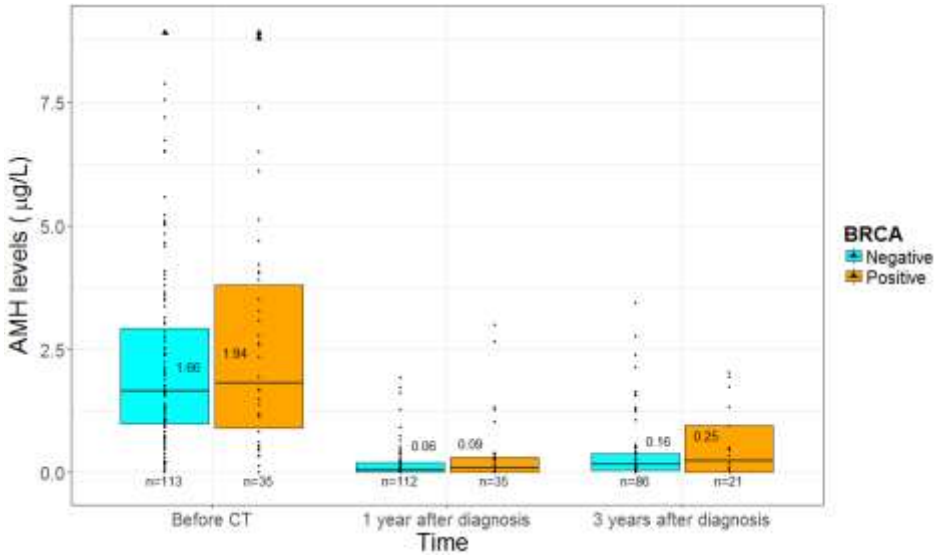
Titus S et al, Sci Transl Med 2013;5:172ra21.
Lambertini M et al, Ann Oncol 2018;29(1):237-43. Son KA et al, Front Endocrinol 2019;10:235

Risk of Treatment-Related POI in *BRCA*-Mutated Breast Cancer Patients

No difference in probability of **CT-induced amenorrhea** between *BRCA*-carriers and noncarriers

No difference in post-chemotherapy **AMH levels** between *BRCA*-carriers and noncarriers





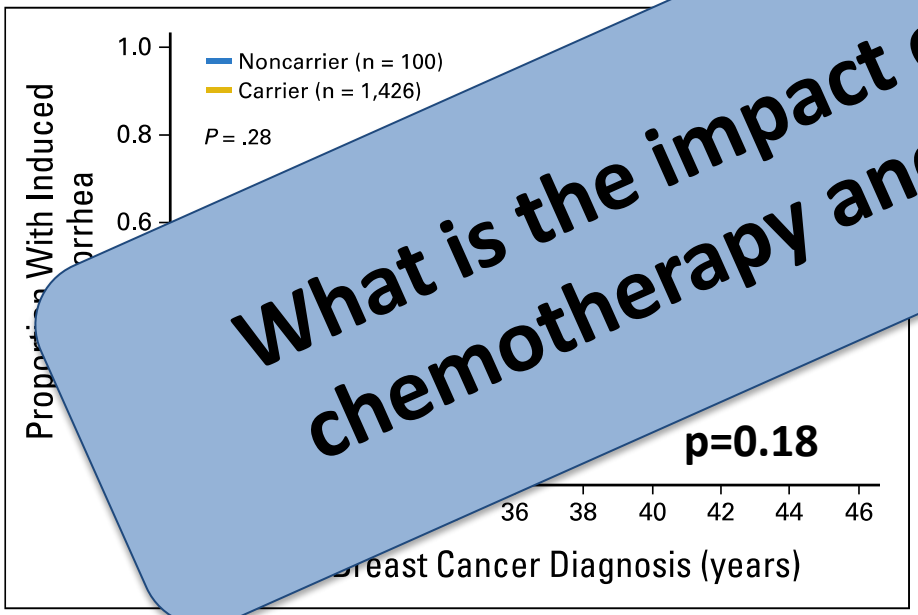
Valentini A et al, J Clin Oncol 2013; 31:3914-9. Lambertini M et al, Front Oncol 2019;9:575

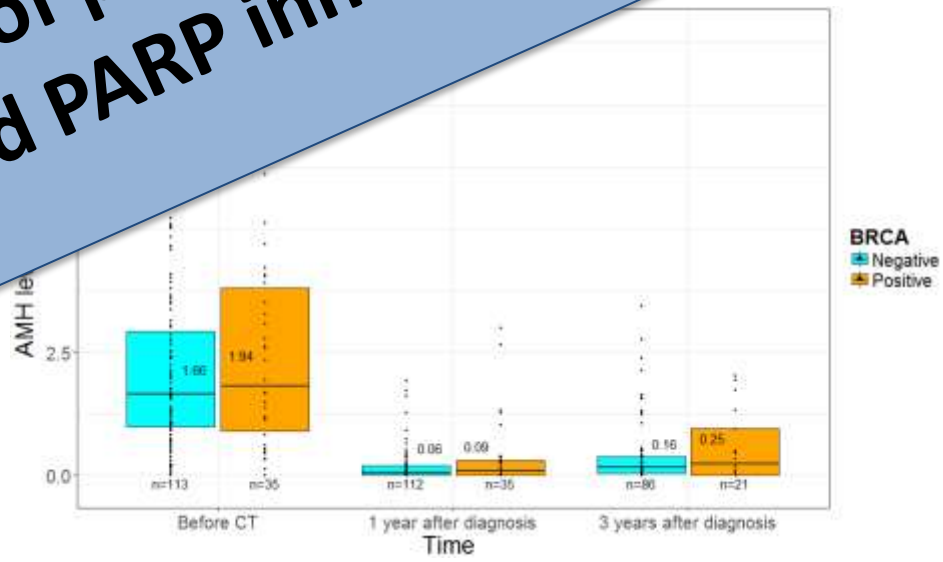
Risk of Treatment-Related POI in *BRCA*-Mutated Breast Cancer Patients

No difference in probability of **CT-induced amenorrhea** between *BRCA*-carriers and noncarriers

No differen **rapy**

What is the impact of platinum-based chemotherapy and PARP inhibitors ?





Valentini A et al, J Clin Oncol 2013; 31:3914-9. Lambertini M et al, Front Oncol 2019;9:575

Available Strategies for Fertility Preservation in Breast Cancer Patients

Type of strategy	Definition	Experimental or standard strategy	Ovarian stimulation required	Delay in the initiation of cancer therapy	Surgery required	Preservation of ovarian function
Oocyte cryopreservation	Harvesting and freezing of unfertilized eggs	Standard	Yes	Yes	Yes	No
Embryo cryopreservation	Harvesting eggs, *in vitro* fertilization, and freezing of embryos	Standard (Not permitted in Italy)	Yes	Yes	Yes	No
Ovarian tissue cryopreservation	Freezing of ovarian tissue and reimplantation after cancer treatment	Experimental	No	No	Yes	Yes
Ovarian suppression with GnRHa	Use of hormonal therapies to protect ovarian tissue during chemotherapy.	Standard*	No	No	No	Yes

*** For ovarian function preservation**

Peccatori F et al, Ann Oncol 2013;24:vi160-70. Oktay K et al, J Clin Oncol 2018;36(19):1994-2001. Paluch-Shimon S et al, Breast 2017;35:203-17. Lambertini M et al, Eur J Cancer 2017;71:25-33. Kim J et al, J Clin Endocrinol Metab 2016;101:1364-71. Oktay K et al, J Clin Oncol 2015;33:2424-9. Diaz-Garcia C et al, Fertil Steril 2018;109(3):478-85 Lambertini M et al, Ann Oncol 2015; 26:2408-19. Lambertini M et al, J Clin Oncol 2018;36(19):1981-90

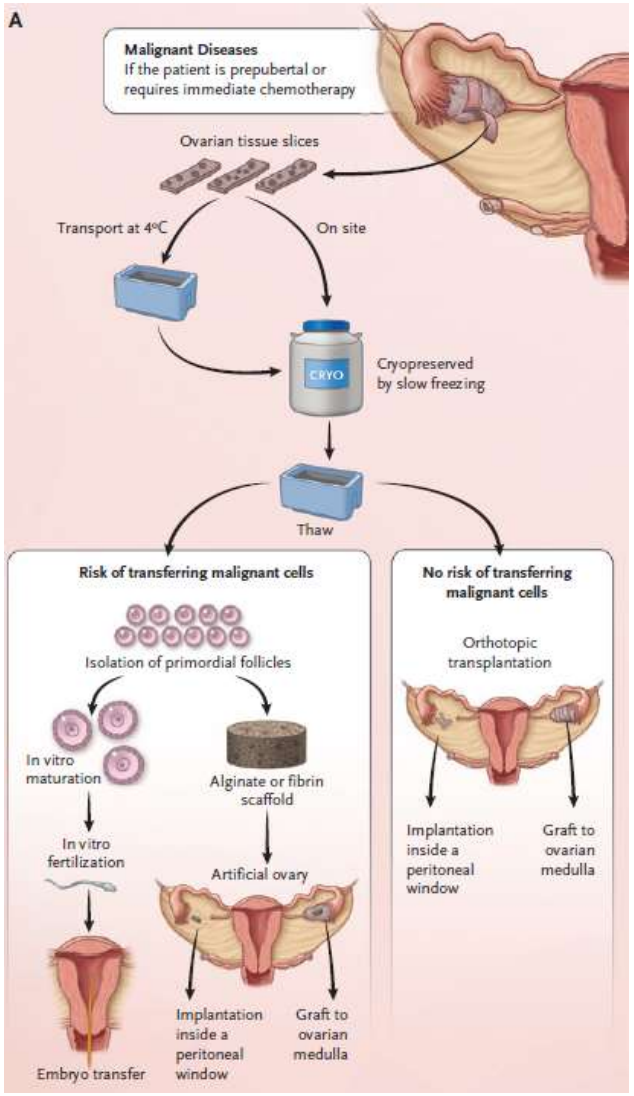
Oocyte(Embryo) Cryopreservation in *BRCA*-Mutated Breast Cancer Patients

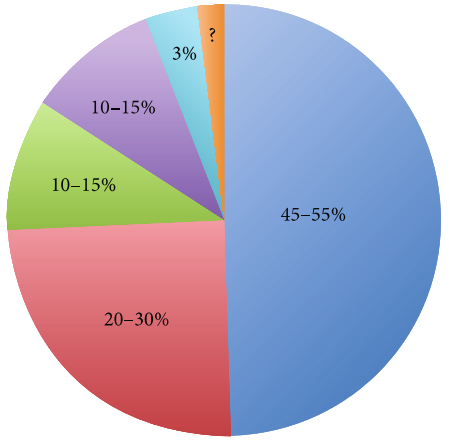
It is not possible to exclude that oocyte(embryo) cryopreservation has lower performance in *BRCA*-mutated breast cancer patients than non carriers

Study	*BRCA+* No.	*BRCA-* No.	Collected oocytes *BRCA+* vs. *BRCA-*
Shapira et al. 2015	20	36	11.5 (6.63) vs. 11.69 (7.23) p = 0.92
Lambertini et al. 2018	**10**	**19**	**6.5 (3 – 7) vs. 9 (5 – 13) p = 0.145**
Turan V et al. 2018	**21**	**97**	**11.0 (8.0) vs. 16.4 (7.7) p = 0.015**
Gunnala V et al. 2019	38	53	14.4 (9.1) vs. 13.1 (8.4) p = 0.747

Shapira M et al, J Assist Reprod Genet 2015;32:1171-8. Lambertini M et al, Ann Oncol 2018;29(1):237-43
Turan V et al, Reprod Sci 2018;25(1):26-32. Gunnala V et al, Fertil Steril 2019;111(2):363-71

Ovarian Tissue Cryopreservation in *BRCA*-Mutated Patients: Is it Safe?





To be considered only in patients diagnosed at a very young age who cannot perform embryo/oocyte cryopreservation

Donnez J & Dolmans MM, N Engl J Med 2017;377(17):1657-65.
Toss A et al, Biomed Res Int 2015;2015:341723. Lambertini M et al, Cancer Treat Rev 2017;59:61-70

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- Introduction
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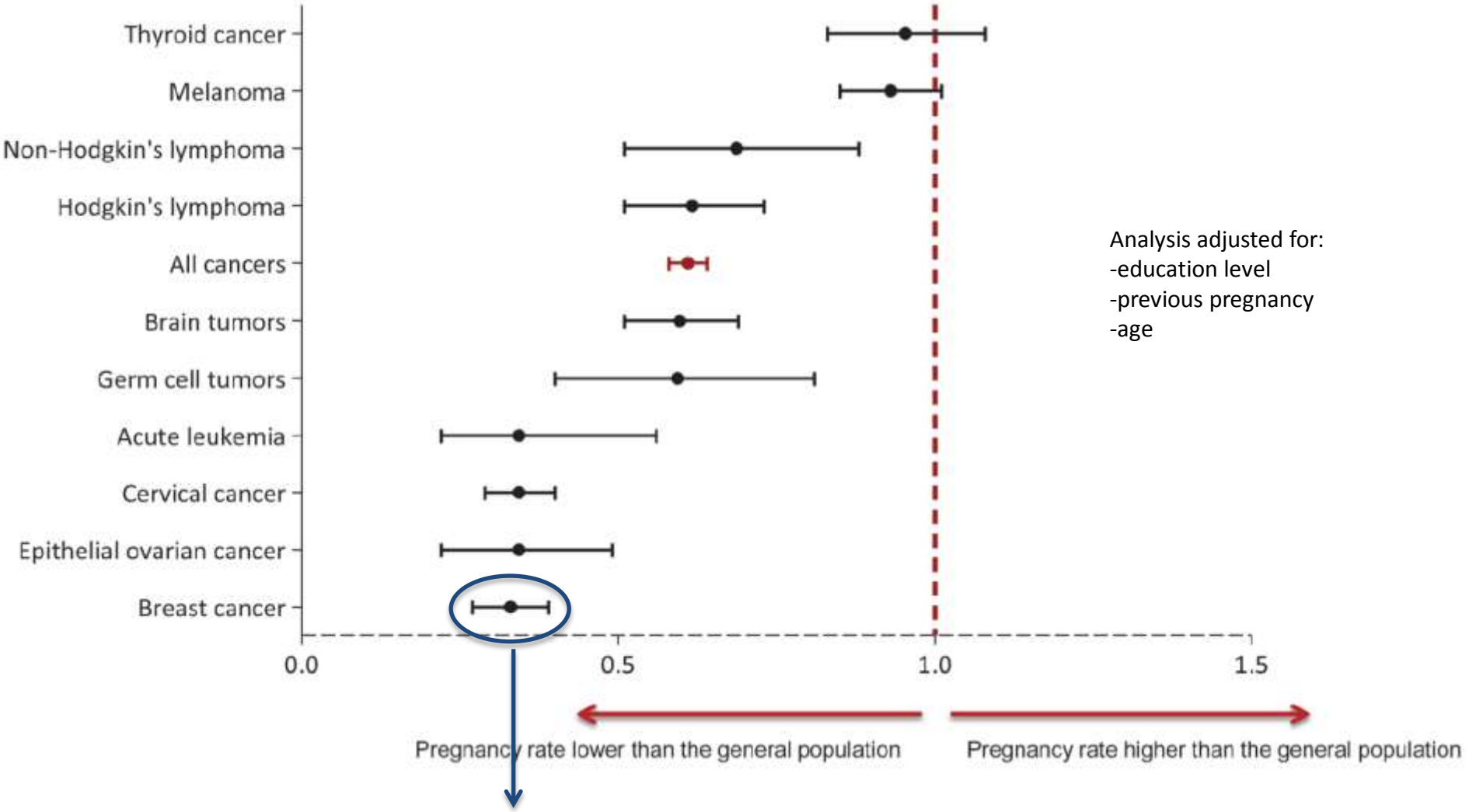
- **Safety of pregnancy after breast cancer in patients with *BRCA* mutations**
- Conclusions

Pregnancy after Breast Cancer

Breast cancer patients have the lowest chances among cancer survivors to become subsequently pregnant !



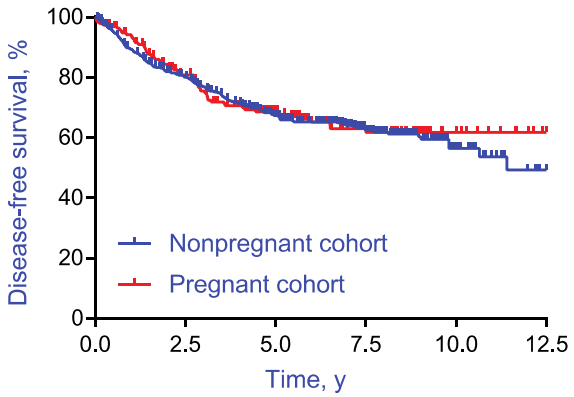
70% lower chance of pregnancy compared to general population

Peccatori F et al, Ann Oncol 2013;24:vi160-70

Pregnancy after Breast Cancer – Is It Safe for the Mother?

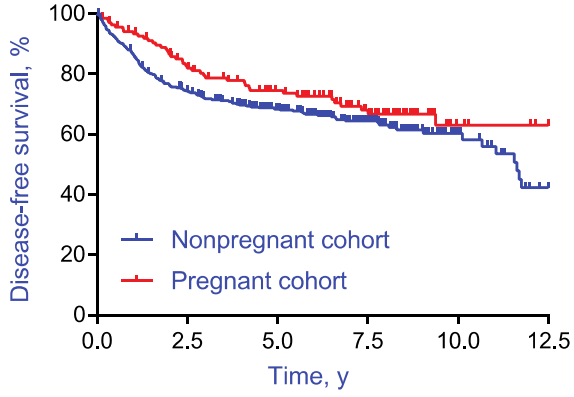
DFS

ER+



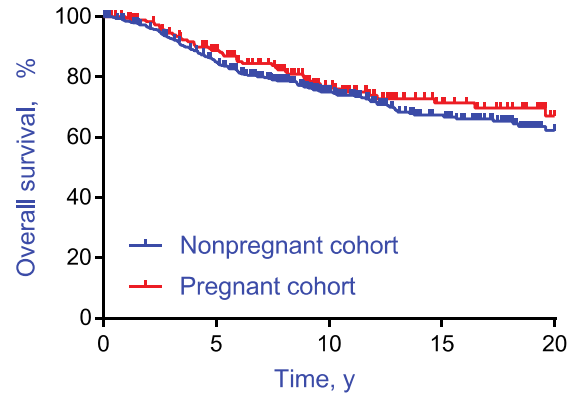
No. at risk						
Nonpregnant	492	346	233	134	32	5
Pregnant	194	138	88	50	17	4

ER-

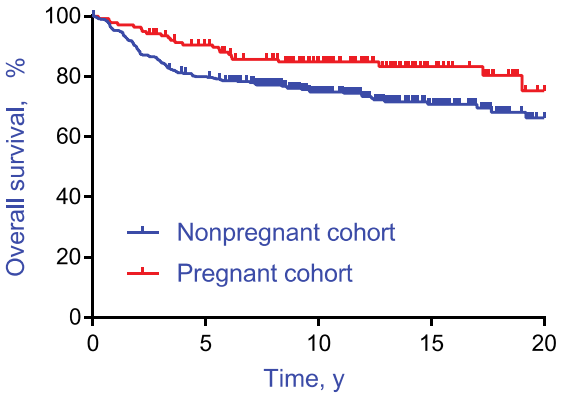


No. at risk						
Nonpregnant	382	264	200	112	30	11
Pregnant	139	105	81	52	12	8

OS



No. at risk						
Nonpregnant	492	381	213	114	48	
Pregnant	194	148	86	48	24	



No. at risk						
Nonpregnant	382	296	179	80	31	
Pregnant	139	117	77	35	13	

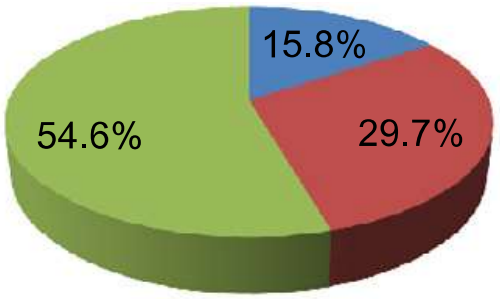
Lambertini M et al, J Natl Cancer Instit 2018;110:426-9

Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

A BCY3/ BCC 2017 survey on physicians' knowledge, attitudes and practice on fertility and pregnancy issues in young breast cancer patients

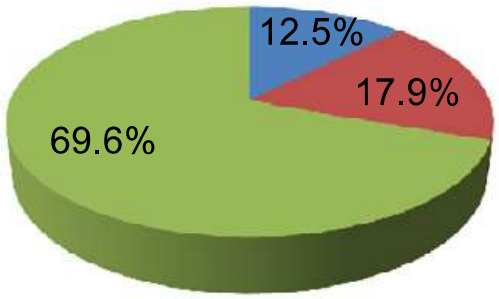
May a pregnancy in breast cancer survivors increase the risk of recurrence ?

***BRCA*-mutated breast cancer**



P<0.001

Breast cancer overall

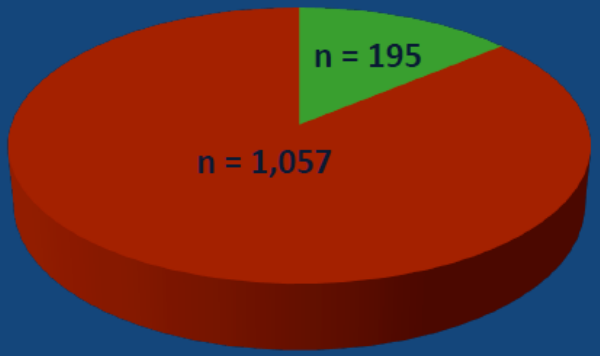


Lambertini M et al, Reprod Biomed Online 2019; 38(5):835-44

Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

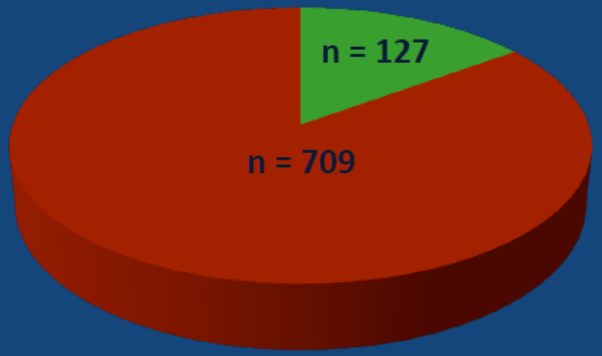
Pregnancy Rate

Overall study population
n = 1,252



16% (95% CI, 14% - 18%)

Centers with ≥ 50 patients
n = 836



15% (95% CI, 13% - 18%)

Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

Pregnancy, Fetal and Obstetrical Outcomes

Median age at the time of pregnancy = 35.7 years (IQR, 32.9–38.6)

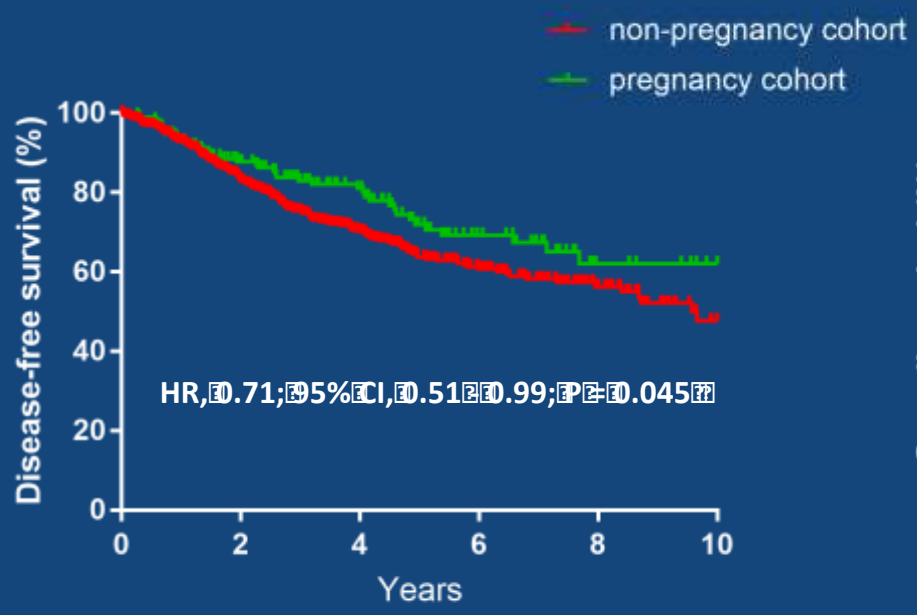
Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

Pregnancy, Fetal and Obstetrical Outcomes

	Pregnancy cohort: n = 195 N (%)
Type of conception:	
Spontaneous pregnancy	133 (82.1)
Use of assisted reproductive technology	29 (17.9)
Missing	33
Pregnancy outcome:	
Completed pregnancy	150 (76.9)
Ongoing pregnancy	7 (3.6)
Induced abortion	16 (8.2)
Spontaneous abortion	20 (10.3)
Unknown outcome	2 (1.0)
Number of live births at the first pregnancy after breast cancer:	
1	130 (86.7)
2	20 (13.3)
Timing of delivery:	
At term (≥37 weeks)	108 (90.8)
Preterm (<37 weeks)	11 (9.2)
Missing	31
Pregnancy complications:	
None	97 (86.6)
Delivery complications	13 (11.6)
Congenital abnormalities	2 (1.8)
Missing	38
Breastfeeding:	
No	58 (65.2)
Yes	31 (34.8)
Missing	61
Duration of breastfeeding, median (IQR), months:	6 (2 - 10)
Missing	5

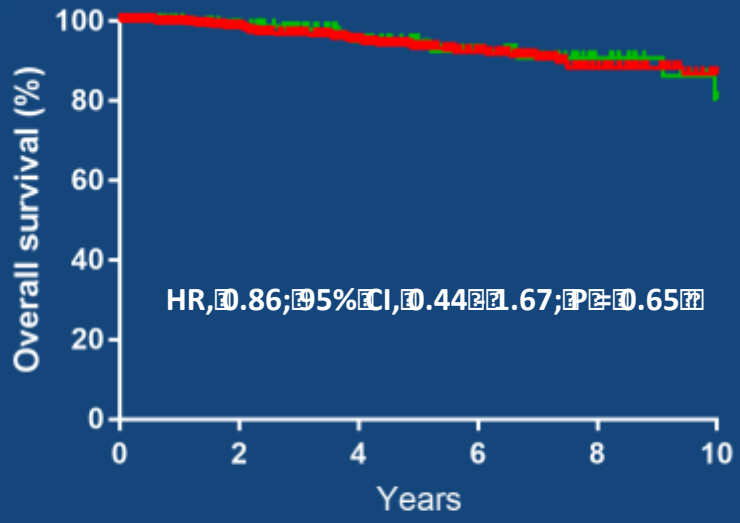
Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

Disease-Free Survival



No. at risk						
non-pregnancy cohort	528	336	198	114	53	19
pregnancy cohort	176	119	80	41	17	10

Overall Survival



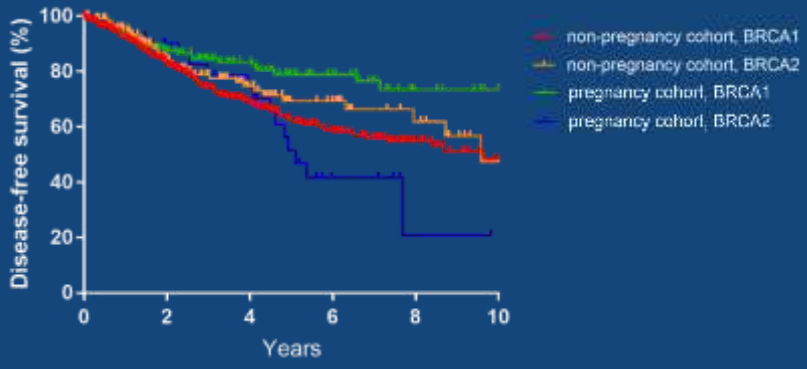
No. at risk						
Non pregnant	528	401	278	181	97	51
Pregnant	176	136	96	62	30	14

Pregnancy after Breast Cancer – Is It Safe in *BRCA*-Mutated Patients?

Disease-Free Survival: Subgroup Analysis

Median follow-up = 8.3 years (IQR, 8.1–8.7)

Type of *BRCA* mutation



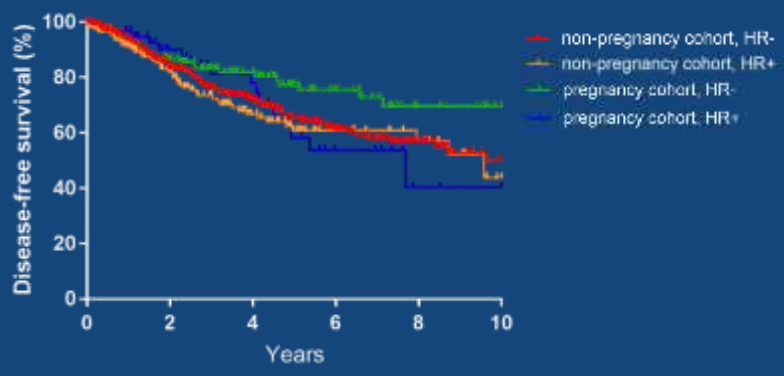
No. at risk						
Non pregnant, BRCA1	393	256	150	87	39	16
Non pregnant, BRCA2	134	80	48	27	14	3
Pregnant, BRCA1	130	93	61	35	16	10
Pregnant, BRCA2	44	25	18	5	1	0

P for interaction = 0.01

BRCA1: HR, 0.53; 95% CI, 0.35–0.81

BRCA2: HR, 1.60; 95% CI, 0.86–2.89

Hormone receptor status



No. at risk						
Non pregnant, HR-	348	235	146	88	38	16
Non pregnant, HR+	180	101	52	26	15	3
Pregnant, HR-	116	86	58	32	15	9
Pregnant, HR+	60	33	22	9	2	1

P for interaction = 0.28

Hormone receptor-positive: HR, 0.91; 95% CI, 0.52–1.60

Hormone receptor-negative: HR, 0.62; 95% CI, 0.40–0.95

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- **Conclusions**

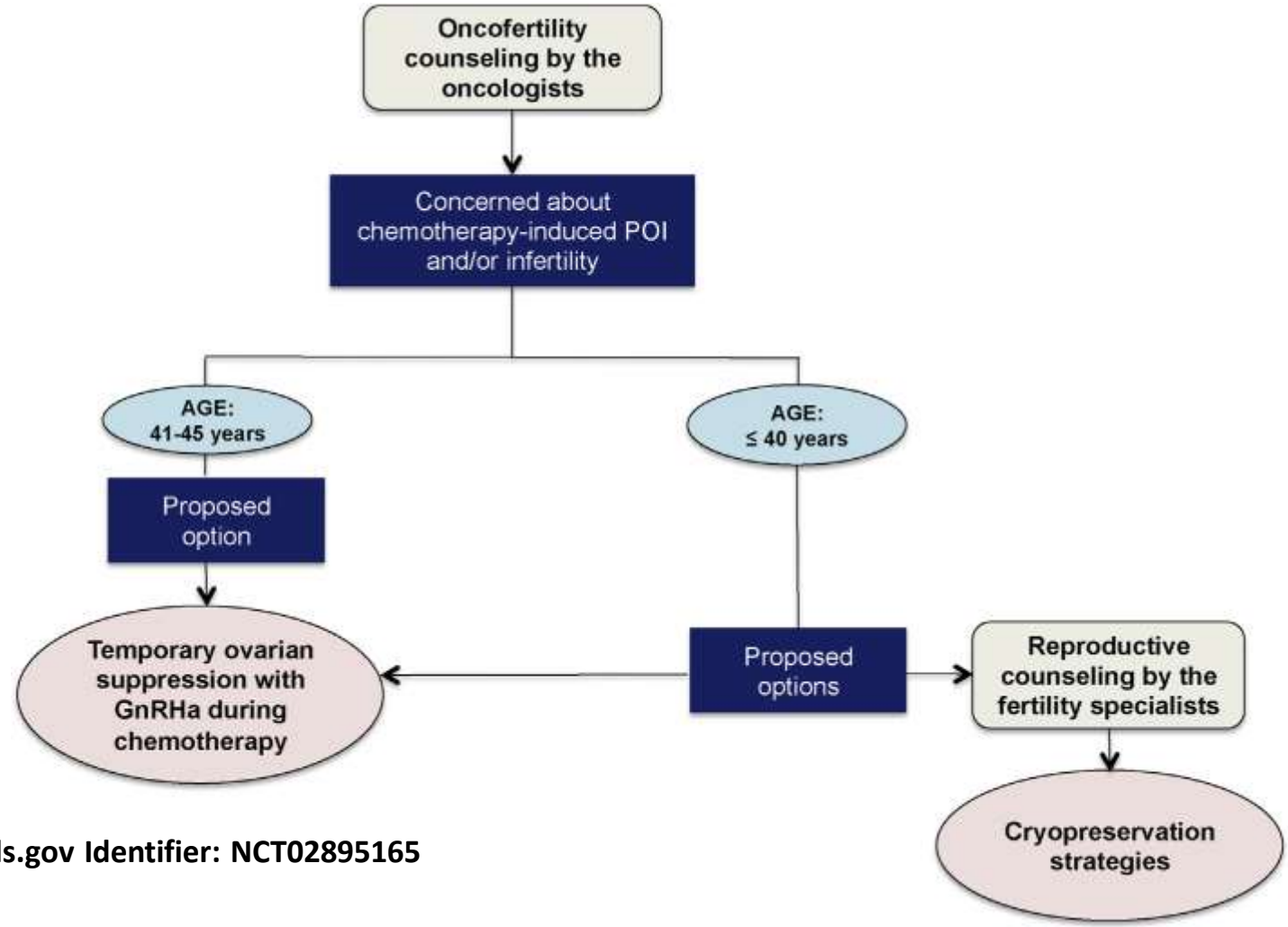
Conclusions

- **Oncofertility counseling is mandatory: the presence of a *BRCA* mutation adds additional burden on this regard**

Strategy	Issues in *BRCA*-mutated breast cancer patients	Indication in *BRCA*-mutated breast cancer
Oocyte(embryo) cryopreservation	- Possible lower response to controlled ovarian stimulation - No data on pregnancy and fertility preservation outcomes	Yes (standard)
Cryopreservation of ovarian tissue	- High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years - Limited data on the efficacy and safety of the procedure (only two pregancies reported)	To be considered only in patients diagnosed at a very young age who cannot perform embryo/oocyte cryopreservation
GnRHa during chemotherapy	- High risk of ovarian cancer and prophylactic gynecological surgery recommended between 35 and 40 years - No data on the efficacy and safety of the procedure	To be considered only in patients diagnosed at a very young age

- **After adequate treatment and follow-up, pregnancy after breast cancer is safe including among *BRCA*-mutated patients**

Conclusions
Lo Studio PREFER (PREgnancy and FERtility)



ClinicalTrials.gov Identifier: NCT02895165

Lambertini M et al, BMC Cancer 2016;17(1):346. Lambertini M et al, Breast 2018;41:51-6

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