Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ASST Pavia

ATS Pavia

UNIVERSITÀ DI PAVIA

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

Carcinoma mammario, BRCA e gravidanza: Una relazione complicata

Alberta Ferrari
Responsabile SSD Chirurgia dei Tumori Eredo-famigliari
Dipartimento Chirurgico

SSD Chir. Tumori Eredo-famigliari (from HBOC …. To King Unit)

PDTRA 04.0 2023 aziendale TEMO: Mammella, Ovaio + Pancreas, Prostata

Identificazione soggetto a rischio (Criteri AIOM 2021)

GENETICA – TEST BRCA/Pannello multitest

Gestione TEMO

SSD TEf - BCC

- Amb TEMO senologico
- Chirurgia RR senologico
- Trattamento CM ereditario

Ovaric Cancer Centre

- Amb TEMO ginecologia
- Chir RR ginecologico
- Trattamento CO/gyn ereditari

SSD TEf - Pancreas Unit

- Amb. TE pancreas
- Trattamento CPa ereditario

SSD TEf – SC Urologia

- Amb. TE prostata
- Trattamento CP ereditario

SSD Diagnostica Senologica

- Sorveglianza strumentale

MDM-TEMO

Percorso Psico-oncologico

Background

Donna portatrice di VP BRCA1 / BRCA2:

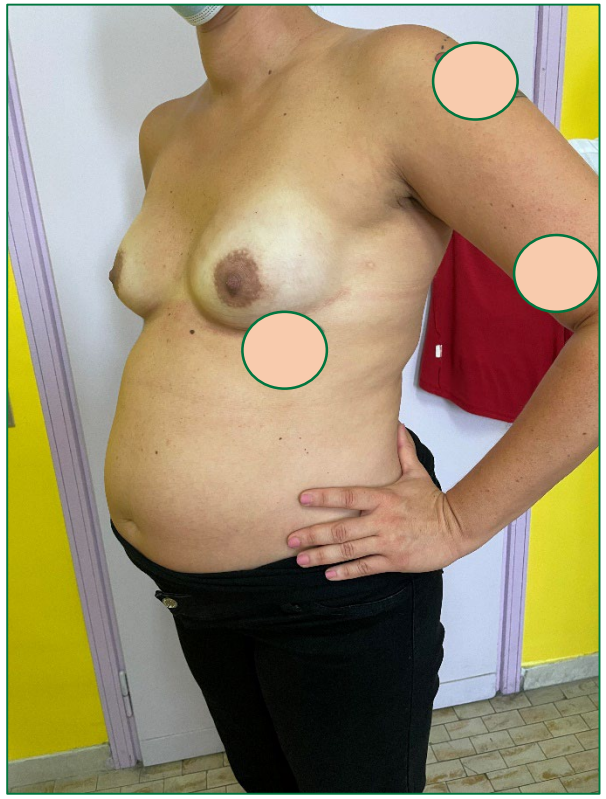
- Alto Rischio ca mammario (CM) 70%
- Alto Rischio ca tuba/ovaio (CO) 44% (BRCA1) – 19% (BRCA2)

Strategie di riduzione del rischio:

- Mastectomia profilattica bilaterale (MRR) 25 – 30 anni vs Sorveglianza
- Annessiectomia bilaterale (AP) a 35-40 (BRCA1) vs 40-45 (BRCA2) anni

Hot Topic in BRCA, senologia e gravidanza:

- CM-BRCA associato (età giovanile, biologia aggressiva) in gravidanza;
- **Gravidanza dopo CM-BRCA** (trattamenti oncologici, safety);
- Finestra di fertilità ristretta (idiopatica, terapie CM, AP).



Giovane donna 33 anni, in esiti MRR, gravidanza VII mese (**previvor**)

Lucia a 62 anni diagnosi OSM di CM di intervallo (screening):
Ca invasivo NAS, G2, Linfo/neuroinvasivo, ER 95%, PR <1%, Ki67 23% c-Erb B2 2+ (FISH non amplificata);
3-06-2015 (altra sede MI) mastectomia + BLS **pT2**(22mm) **pN1**a (1SN-mts massiva; 2SN-micromts) M0. Trattamento adiuvante CHT con antracicline e taxani, programmata ormonoterapia con inibitori dell'aromatasi
OSM 25/03/2016 dissezione ascellare dx (di completamento) pN1 (2/22)

Elisabetta, 35 anni, nel frattempo si sottopone a Mammo/ecografia di controllo:
03/07/15 Mx (OSM): Dx, rare microcalcificazioni ravvicinate Qinf di aspetto benigno, prudenziale controllo mammografico fra 1 anno.
03/08/15 Ecografia mammella (OSM): Dx, lesione focale ipoecogena di 15 mm, poco vascolarizzata, sede parareolare infero-esterna (R4-5). Non linfonodi ascellari patologici.
3/08 Agobiopsia con Esito istologico (OSM): **ca invasivo duttale/NAS, G2, ER>95%, PR>95%, c-Erb B2 1+, Ki67 20%.**

Test Genetico urgente (OSM) esito 16-09: **VP BRCA2** c.522_5225 del

THE GENETIC PATH

Maurizia Grasso, Marilena Tagliani, Davide Bondavalli, Eloisa Arbustini

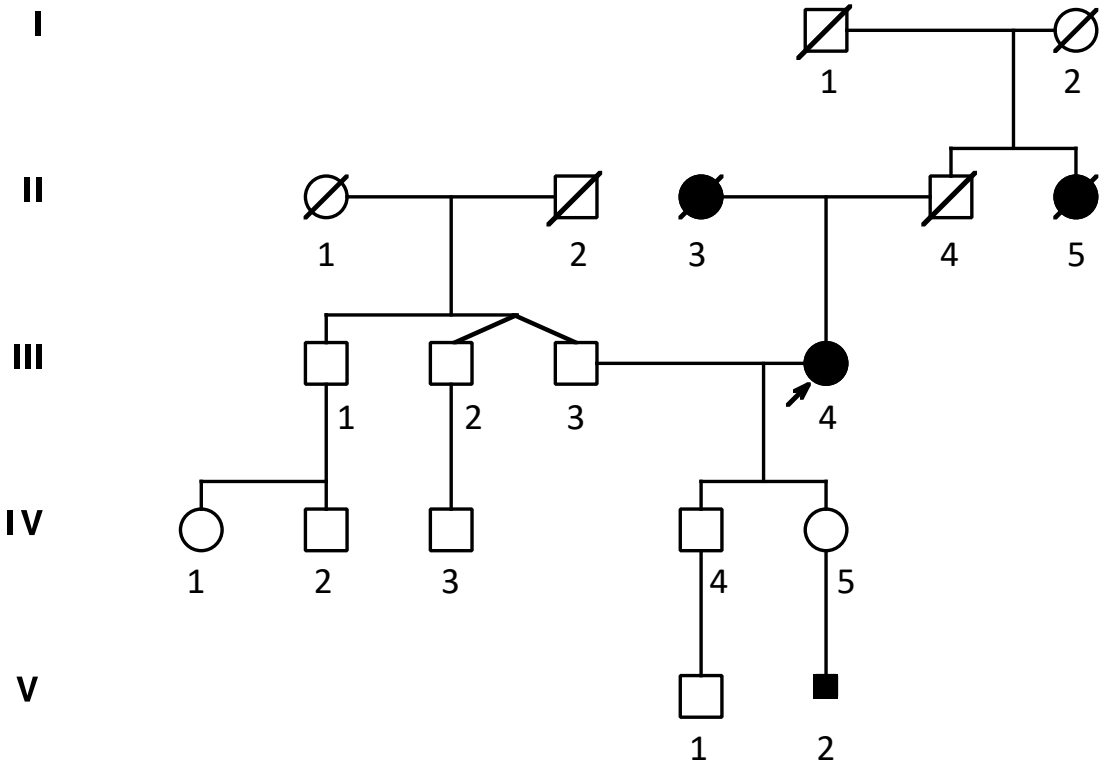
Andrea Pilotto, Carmelina Giorgianni,

Mario Urtis, Michela Ferrari,

Research DPT, IRCCS FOUNDATION, Policlinico San Matteo

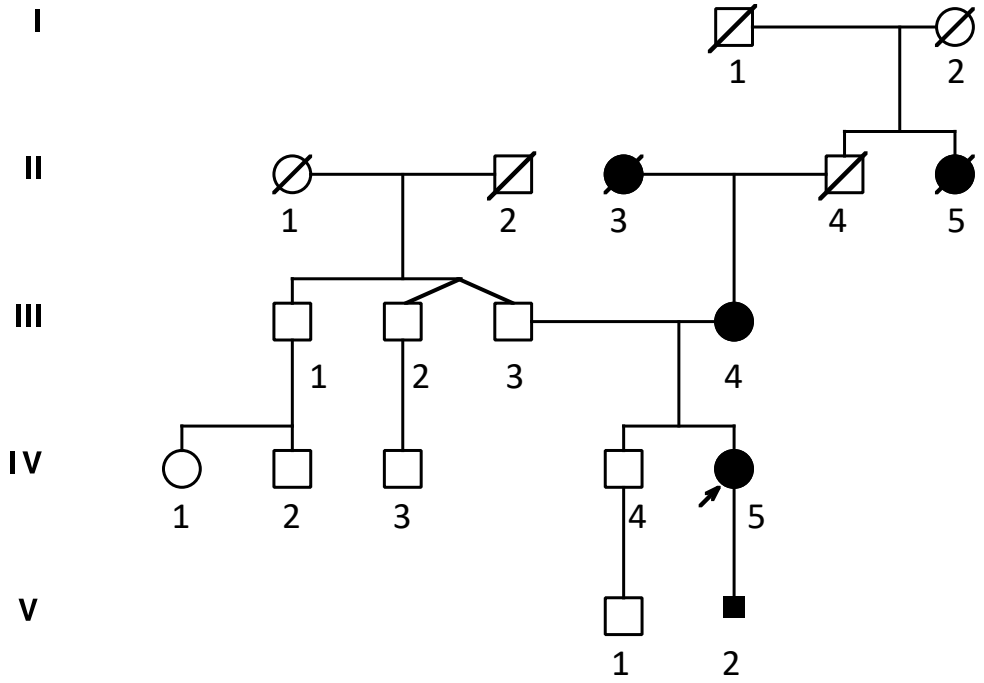
APRIL, 2015 - III:4 → BREAST CANCER, NON-TN - NO GENETIC PATH, 63 yrs

FAMILY MEMBER/S	CLINICAL INFO	STATUS
I:1, I:2	None	Death, old age
II:1 II:2	Histeroannessiectomy at 42; SD, Chronic renal failure;	Death: 90 yrs Death: 42 yrs
II:3	Breast cancer, onset?	Death, 64 yrs
II:4	Biliary peritonitis; emphysema	Death, 80
II:5	Ovarian cancer at 76	Death, 80
III:1, III:2, III:3	Past NHL; prior AMI; achromegalia	64 yrs, Alive
III:2, III:3	Both, IDDM	63 yrs, Alive
III:4	Breast cancer	63 yrs
IV: 1-5	Cancer-free	Age range 30-45
V:1	Healthy	boy
V:2	Miscarriage	< 12 weeks



AUGUST 18th 2015: IV:5 → BREAST CANCER, NON-TN - GENETIC PATH, 35 yrs

FAMILY MEMBER/S	CLINICAL INFO	STATUS
I:1, I:2	None	Death, old age
II:1, II:2	SD,Chronic renal failure; histerlannessiectomy at 42;	Death: 42yrs Death: 90yrs
II:3	**Breast cancer, onset?**	**Death, 64 yrs**
II:4	Biliary peritonitis; emphysema	Death, 80
II:5	**Ovarian cancer at 76**	**Death at 80**
III:1, III:2, III:3	Past NHL; prior AMI; acromegalia	64 yrs, Alive
III:2, III:3	IDDM, both	63 yrs, Alive
III:4	**Brest cancer**	**63 yrs**
IV: 1-4	Cancer free	Age range 30-45
IV:5	**Breast Cancer**	**35 yrs**
V:1	Healthy	boy
V:2	Miscarriage	< 12 weeks

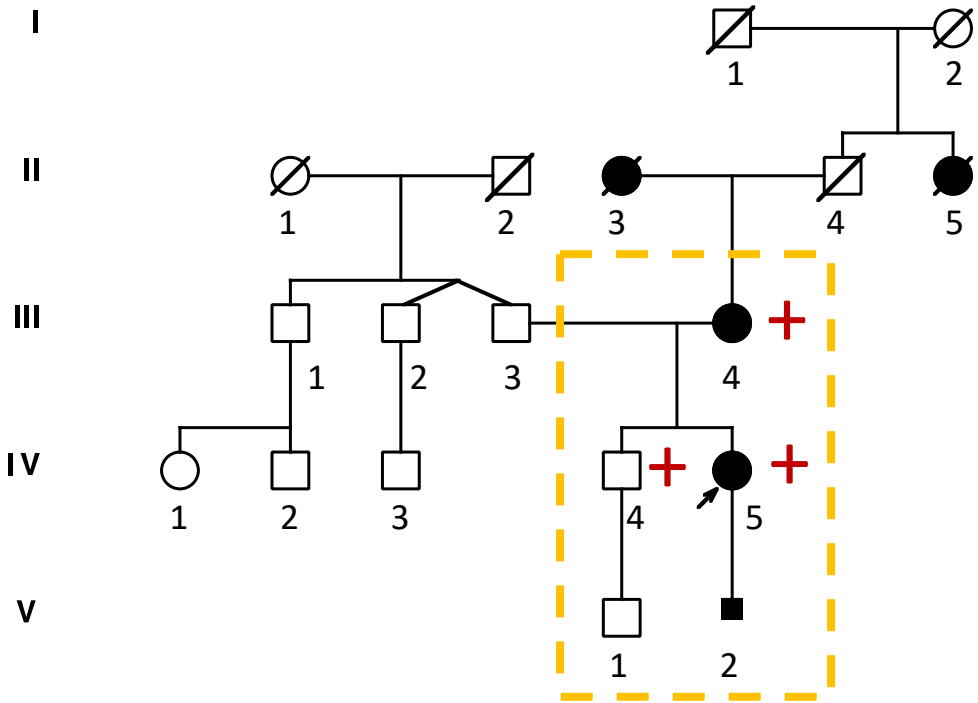


REPORT Sept 18th 2015

BRCA2
c.5222_5225del
*p.Ser1741Thrfs*35, Heterozygous*

COMPLETE GENETIC PATH

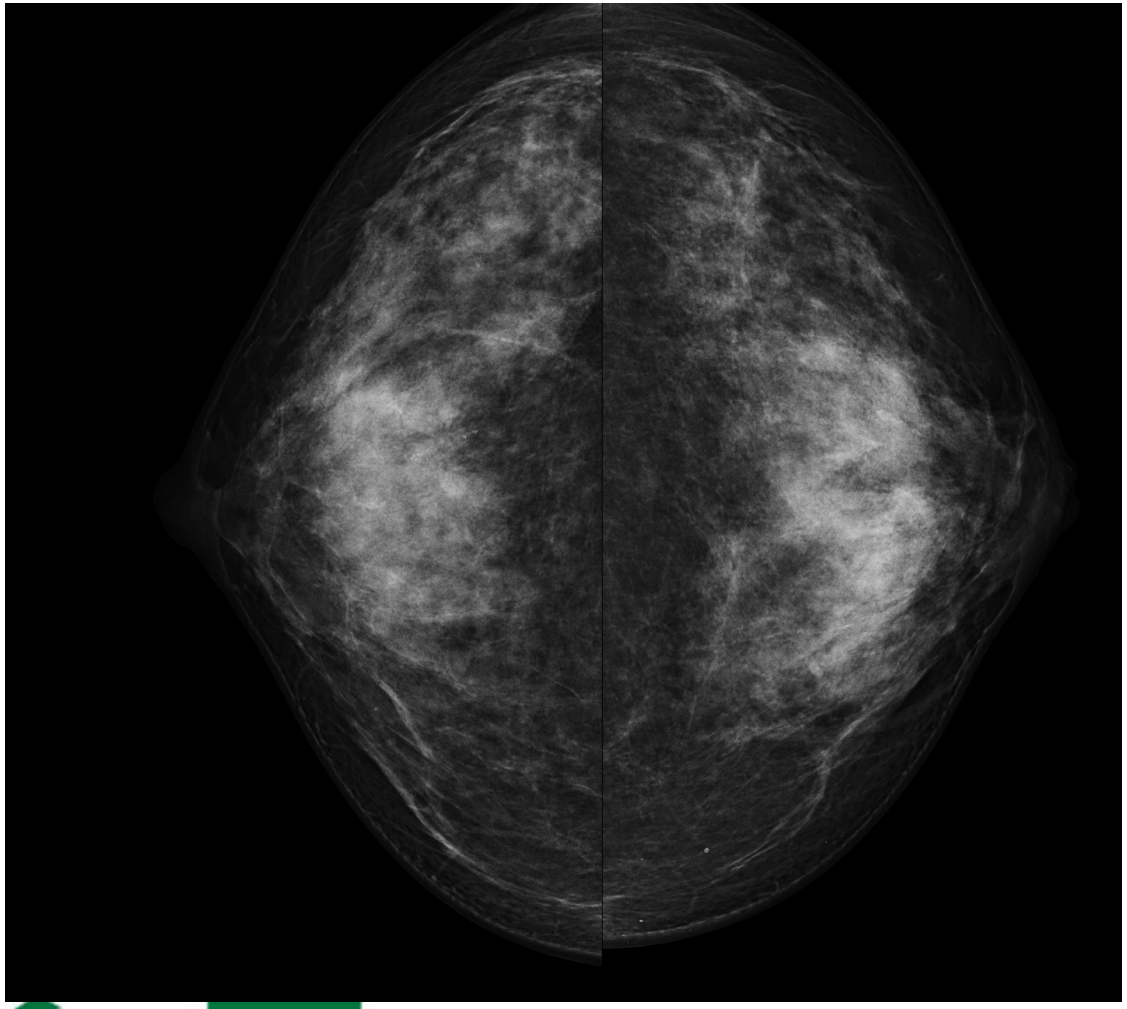
FAMILY MEMBER/S	CLINICAL INFO	STATUS
I:1, I:2	None	Death, old age
II:1, II:2	SD,Chronic renal failure; histerlannessiectomy at 40;	Death: 42yrs Death: 90yrs
II:3	**Breast cancer, onset?**	**Death, 64 yrs**
II:4	Biliary peritonitis; emphysema	Death, 80
II:5	**Ovarian cancer at 76**	**Death at 80**
III:1, III:2, III:3	Past NHL; prior AMI; achromegalia	64 yrs, Alive
III:2, III:3	IDDM	63 yrs, Alive
III:4	**Brest cancer , genetic test +**	**63 yrs**
IV: 1-3	Cancer free	Age range 30-45
IV:4	**Breast cancer, genetic test +**	**35 yrs**
IV:5	**Cancer-free, genetic test +**	**43 yrs**
V:1	healthy	boy
V:2	miscarriage	< 12 weeks

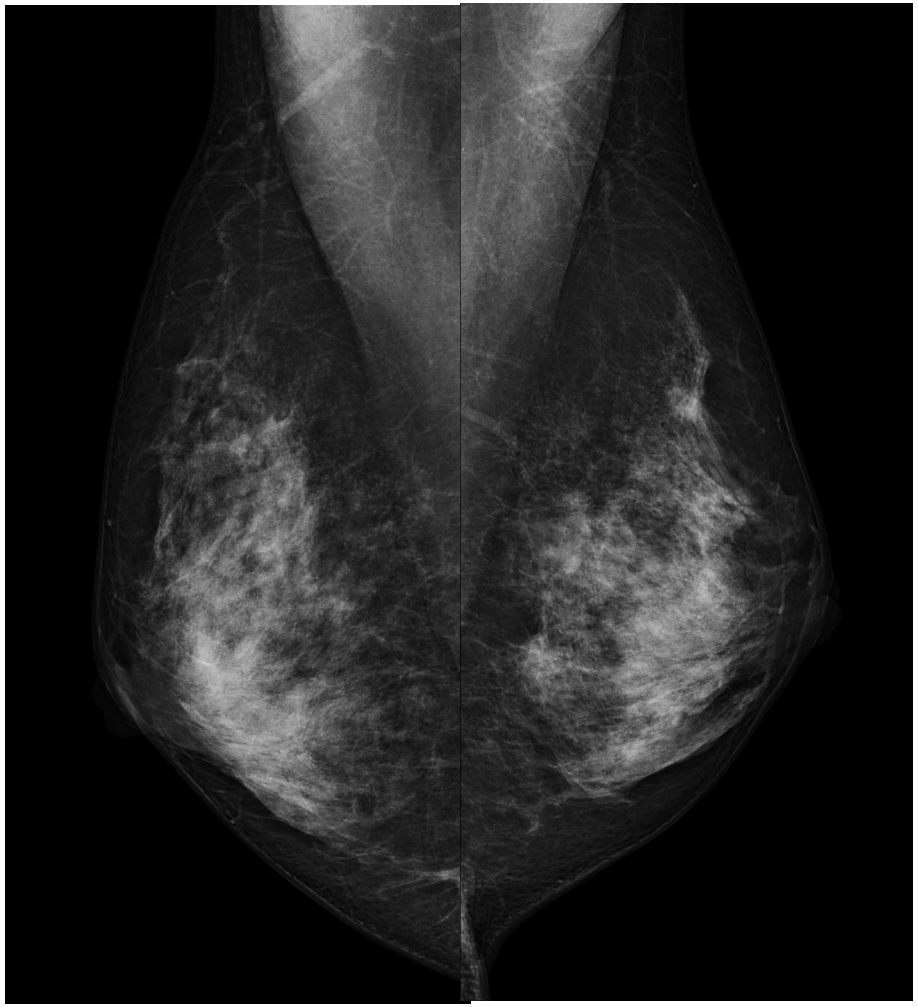


IN GENERAL …GUIDELINES

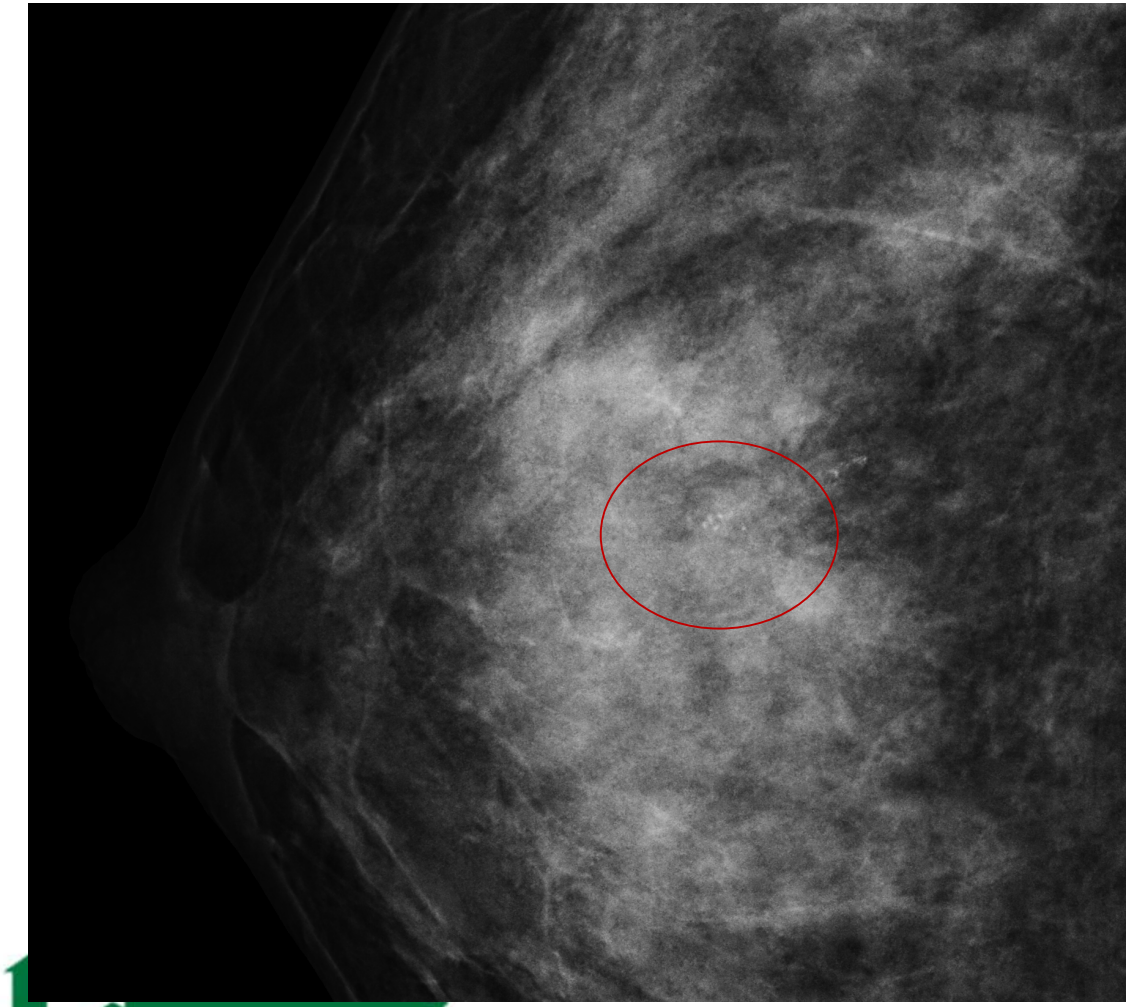
- GUIDELINES EVALUATE AND SUMMARIZE AVAILABLE EVIDENCE WITH THE AIM OF ASSISTING…
- GUIDELINES DO NOT OVERRIDE THE INDIVIDUAL RESPONSIBILITY OF HEALTH PROFESSIONALS…
- Guidelines **represent the official position of the …Given Scientific Society…** on a given topic and are regularly updated.
- The **Members** of the GL Task Force … **selected by the …** to represent professionals involved with the medical care of patients with this pathology
- The experts of the writing and reviewing panels provided **declaration of interest** forms …
- The … Clinical Practice Guidelines (CPG) Committee **supervises and co-ordinates**…
- **Off-label** use of medication … sufficient level of evidence … medically appropriate for a given condition
  - …the **final decisions** concerning an individual patient must be made by the **responsible health professional**

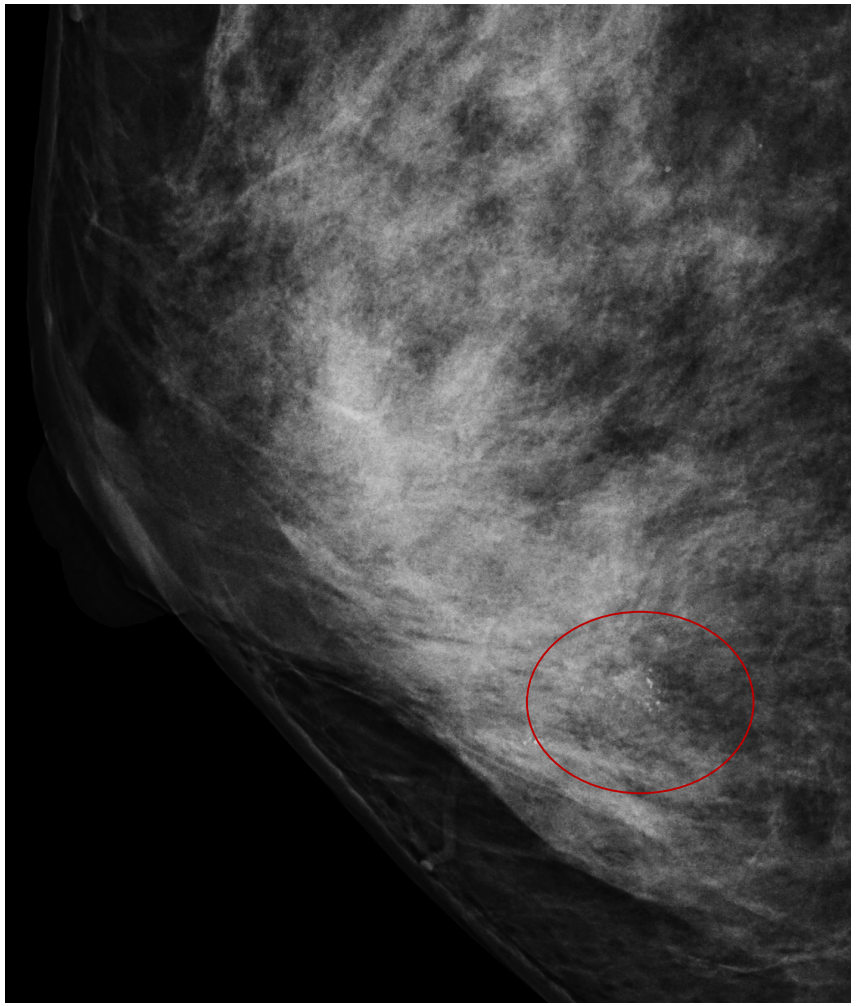
IMAGING Elisabetta

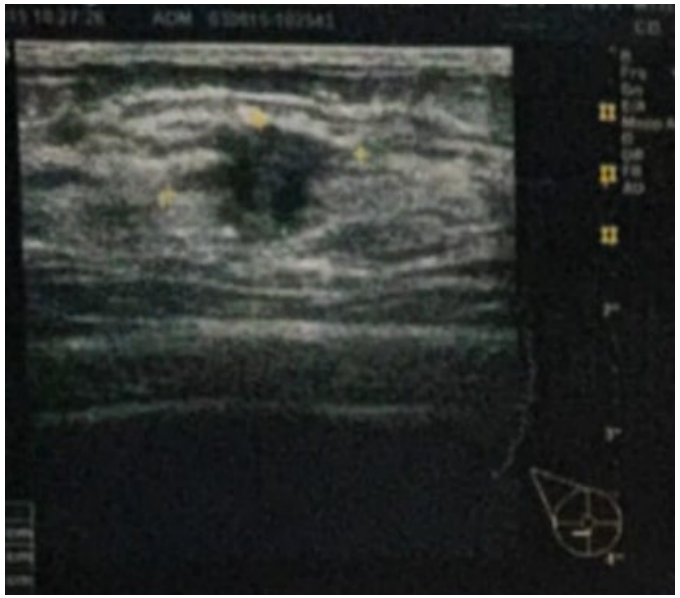




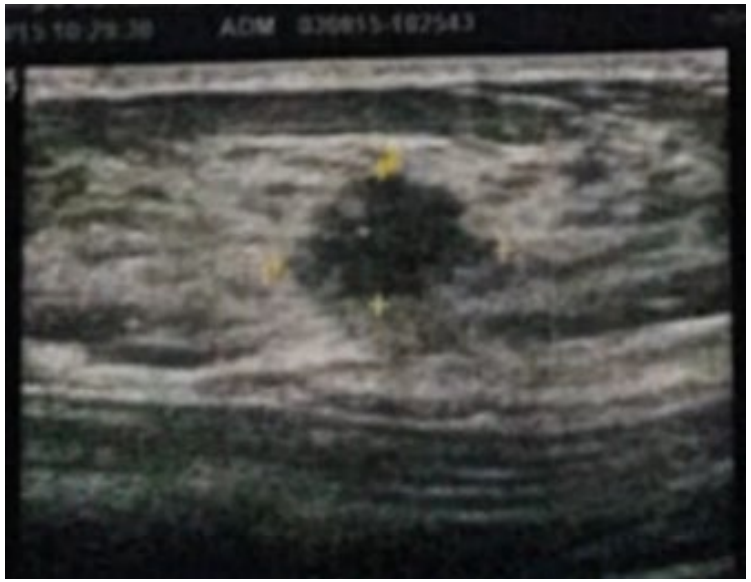
IMAGING Elisabetta

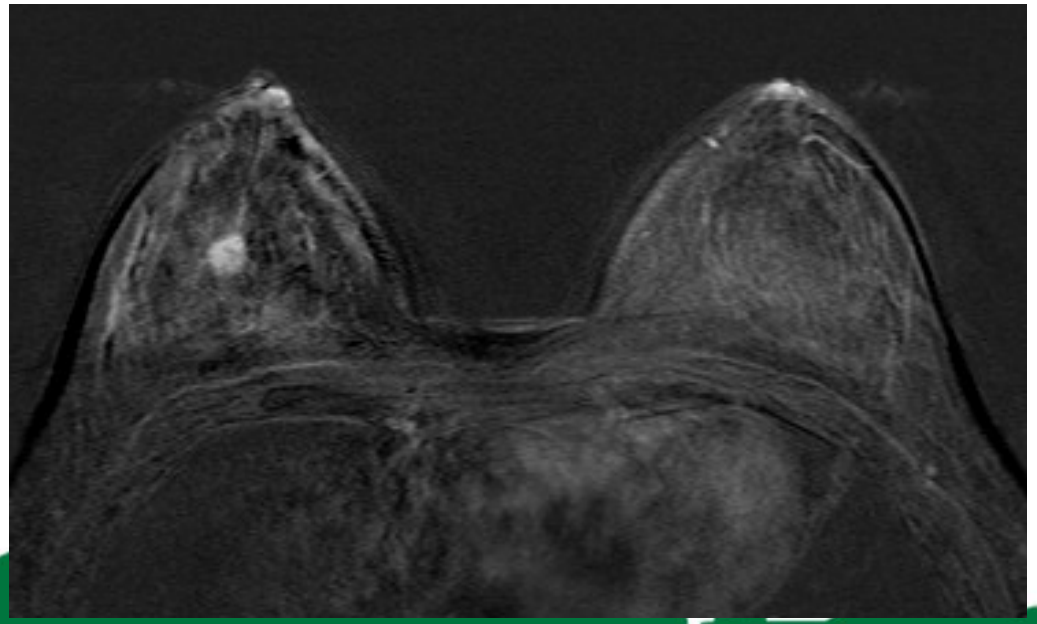


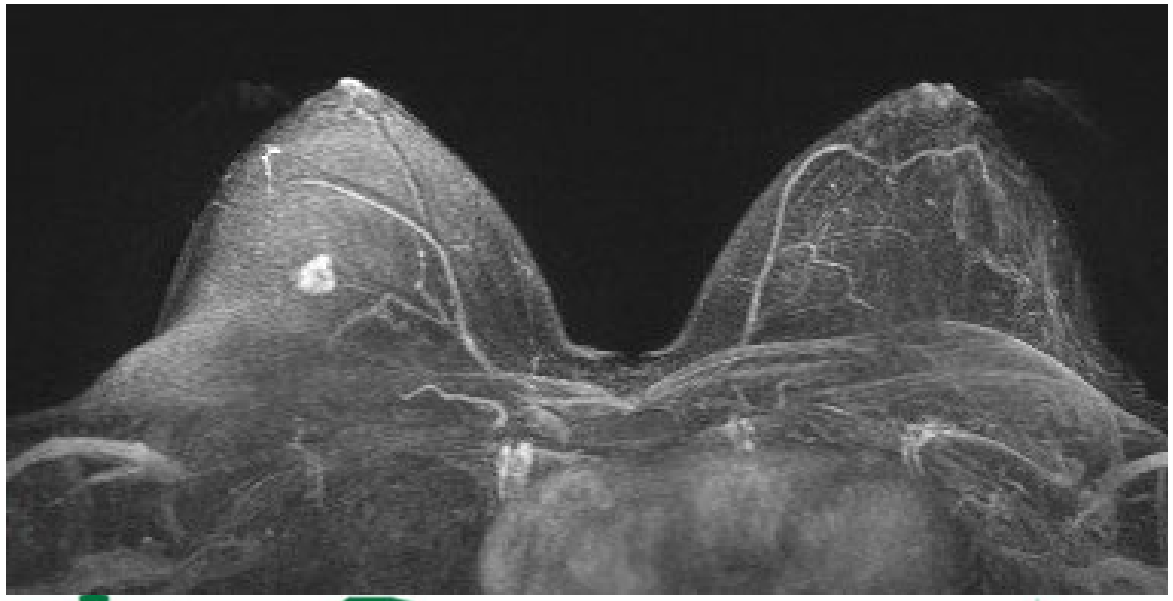




IMAGING Elisabetta



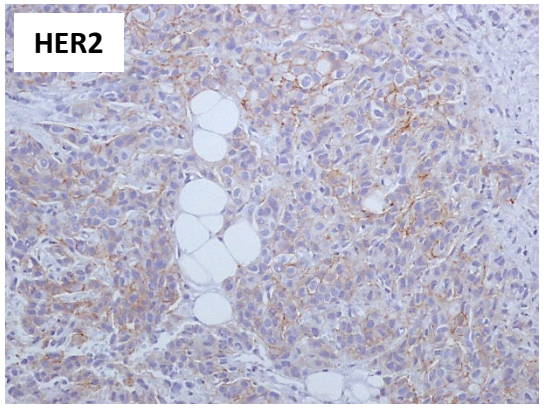


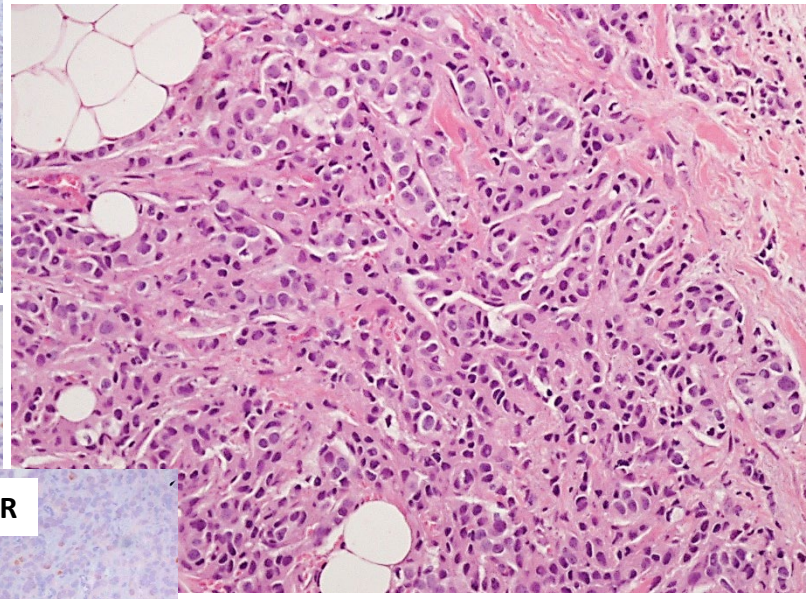


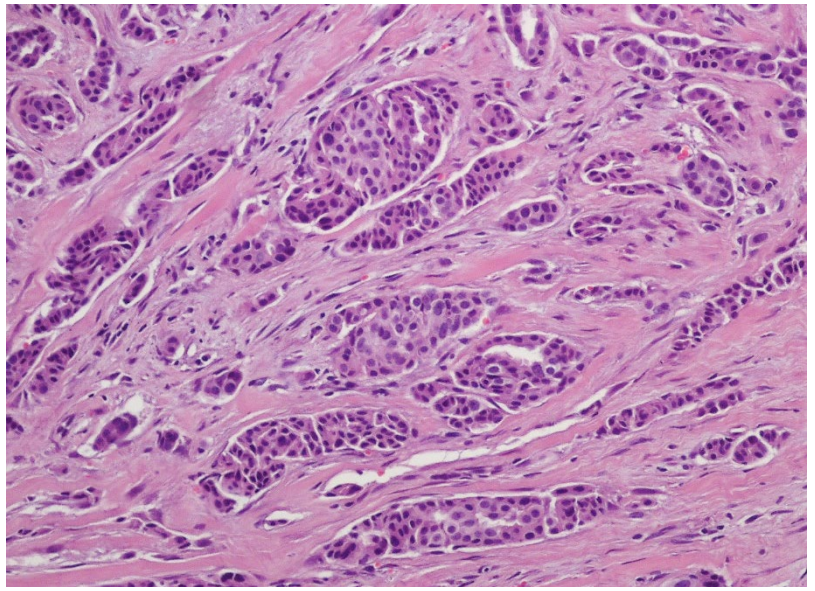
Istologia a confronto

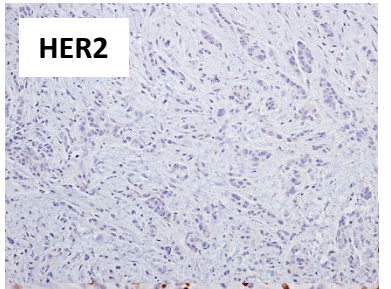
LG

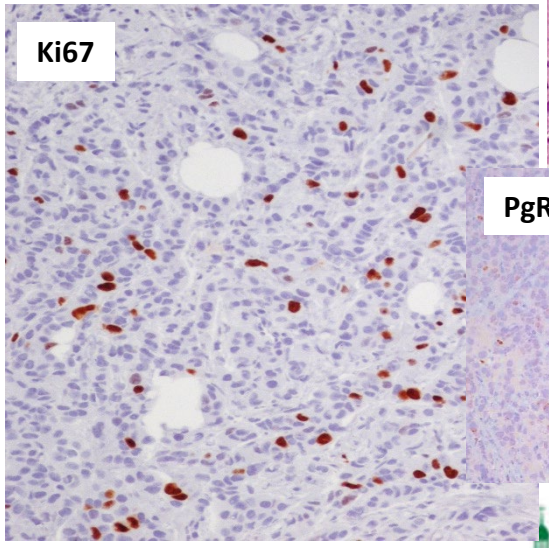
EC

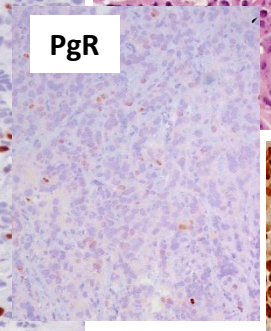


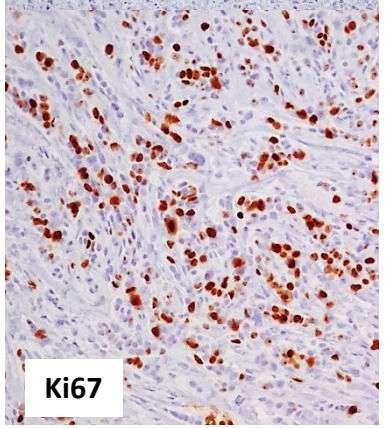


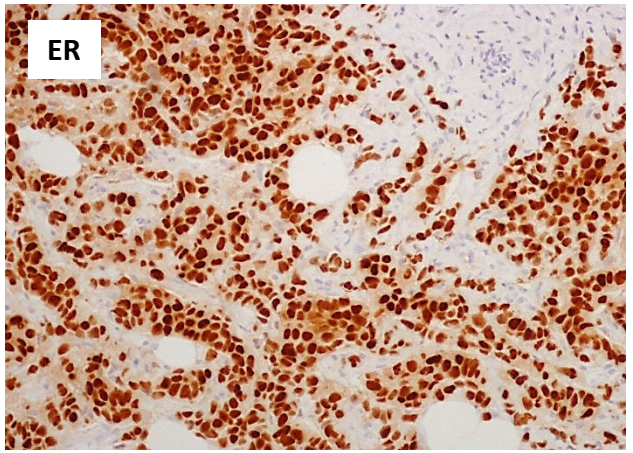


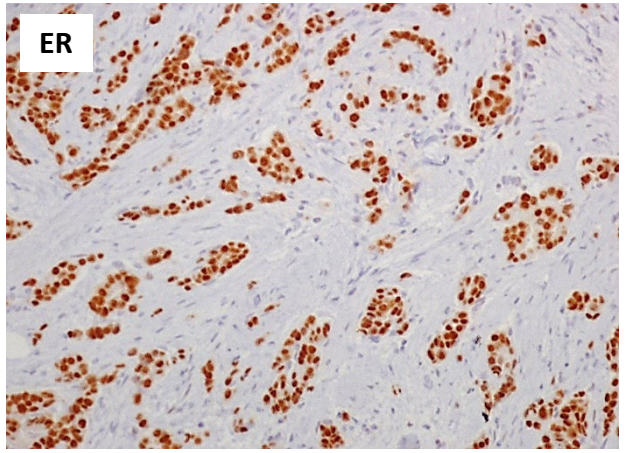


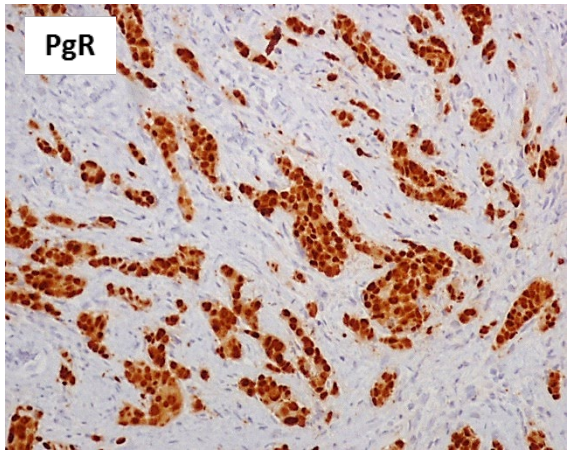












Lucia, 62 anni
CM G2 NAS, Linfo/neuroinvasivo
ER 95%, PR <1%, Ki67 23%
c-Erb B2 2+ (FISH neg)

1. **03/06/15 Mastectomia mono laterale + LS (N+), *altra sede*;**
2. **Chemioterapia adiuvante;**
3. **rimozione espansore (infezione)**
4. **25/03/2016 Dissezione ascella OSM**
   pT2(22mm) **pN1** (2/22) M0.
5. **Terapia Ormonale** per 5 anni.

Novembre 2015: Test Genetico mirato (OSM) positivo per **VP BRCA2** della figlia (caso indice)

09/08/2016 **annessiectomia** profilattica VLP e sorveglianza senologica

Elisabetta, 35 anni
CM G2 NAS, non linfo/neuroinvasivo
ER>95%, PR>95%, Ki67 20%
c-Erb B2 1+ (neg);
VP BRCA2 associato (test urgente)

1. **29/09/15 di Mastectomia nipple-sparing bilaterale (oncologica e RR controlaterale) + LS (esame estemporaneo negativo) e posizionamento bilaterale di protesi mammarie definitive**

FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA
Registro Operatorio
N°. Registro 487

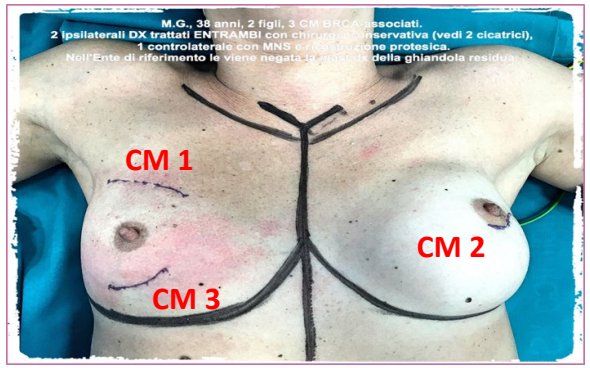
Paziente CAPITTINI ELISABETTA **Sesso** F **Data Nascita** 10/12/1979 **Età** 35 ANNI
Blocco Op. OST/GIN **Spec. Chirurgica** PMA
Sala Op. PMA **Data Intervento** 23/11/2015 **Nosologico** 35054461 **Codice Fiscale** CPTLBT79T50F080V
Regime di Ricovero Day Hospital **Tipologia di Intervento** ELEZIONE

Diagnosi (ICD-9-CM)
628.8 - INFERTILITA FEMMINILE,DI ALTRA ORIGINE SPECIFICATA
Procedure Chirurgiche (ICD-9-CM)
65.91 - ASPIRAZIONE DELL'OVAIO
(aspirazione ovarica ecoguidata)

Crioconservazione ovociti

2. **Terapia ormonale con Tamoxifene**

Chirurgia del CM associato a VP BRCA 1 / 2 – Perché Mastectomia bilaterale



M.G. 29 anni, 2 figli - CM 1 dx: QUART
BRCA1 +
32 anni: CM 2 sin Mast
38 anni: CM 3 dx QUAD
Per 2 volte le viene negata MRR
39 anni (2015): MRR bil in OSM

10 y cumulative incidence of
IBTR: 27% for iBC-BRCA vs **4%** for iBC (p = 0.03)
CBC: 25% for cBC-BRCA vs **1%** for cBC (p= 0,03)

Garcia-Eienne (IEO), 2009

Ann Surg Oncol (2009) 16:3380–3387
DOI 10.1245/s10434-009-0638-7

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast-Conserving Surgery in BRCA1/2 Mutation Carriers: Are We Approaching an Answer?

Carlos A. Garcia-Etienne, MD[1], Monica Barile, MD[2], Oreste D. Gentilini, MD[1], Edoardo Botteri, MSc[3], Nicole Rotmensz, MSc[3], Andrea Sagona, MD[1], Gabriel Farante, MD[1], Viviana Galimberti, MD[1], Alberto Luini, MD[1], Paolo Veronesi, MD[1], and Bernardo Bonanni, MD[2]

[1]Department, European Institute of Oncology, Milan, Italy; [2]Department of Cancer Prevention and ...pean Institute of Oncology, Milan, Italy; [3]Department of Epidemiology and Biostatistics, European Institute ... Milan, Italy

Rischio di Secondo CM!

Mavaddat, 2013

J Natl Cancer Inst. 2013 Jun 5;105(11):812-22. doi: 10.1093/jnci/djt095. Epub 2013 Apr 29.
Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE.
Mavaddat N1, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC, Easton DF; EMBRACE.
The average cumulative risks by age 70 years for BRCA1 carriers were estimated to be 60% (95% confidence interval [CI] = 44% to 75%) for breast cancer, 59% (95% CI = 43% to 76%) for ovarian cancer, and 83% (95% CI = 69% to 94%) for contralateral breast cancer. For BRCA2 carriers, the corresponding risks were 55% (95% CI = 41% to 70%) for breast cancer, 16.5% (95% CI = 7.5% to 34%) for ovarian cancer, and 62% (95% CI = 44% to 79.5%) for contralateral breast cancer.

BRCA2: rischio cumulativo cBC a 70: **62%**

Metcalfe, 2011

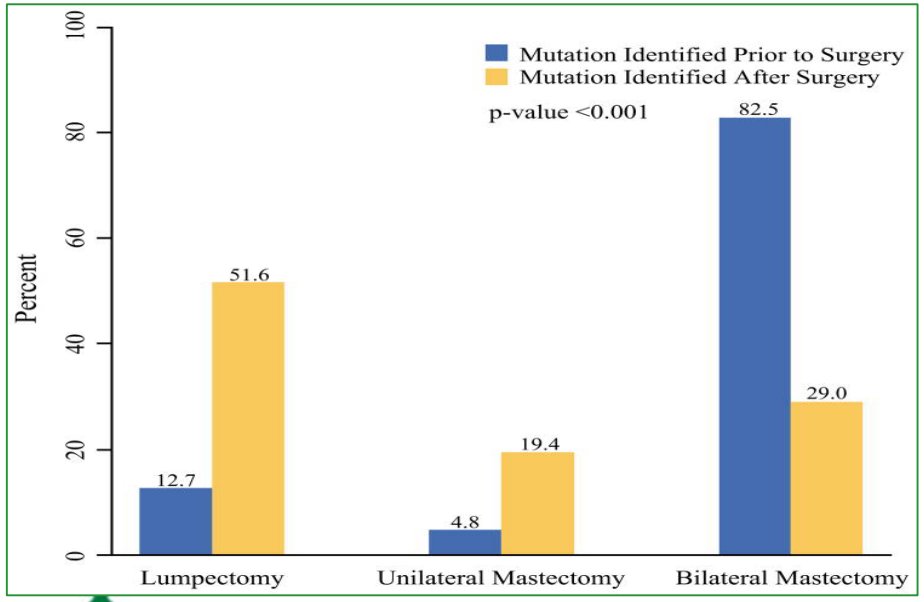
Years from diagnosis	All subjects (%)	BRCA1 (%)	BRCA2 (%)	< 50 years at diagnosis (%) Elisabetta	> 50 years at diagnosis (%) Lucia
5	13.1	13.7	12.0	14.2	8.6
10	22.0	23.8	18.7	23.9	14.7
15	33.8	36.1	28.5	37.6	16.8

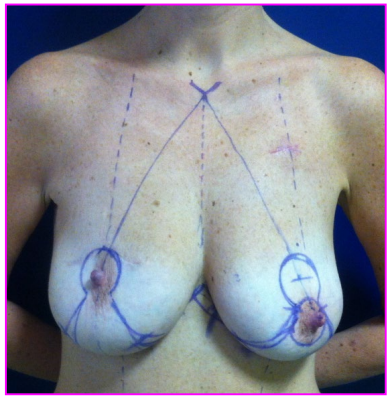
CHIRURGIA Oncologica in CM-BRCA: attenzione al TIMING del test!

Ann Surg Oncol. 2016 Oct;23(10):3232-8. doi: 10.1245/s10434-016-5328-7. Epub 2016 Jun 23.

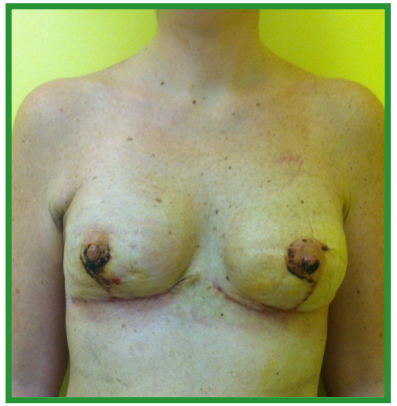
Impact that Timing of Genetic Mutation Diagnosis has on Surgical Decision Making and Outcome for BRCA1/BRCA2 Mutation Carriers with Breast Cancer.

Chiba A[1], Hoskin TL[2], Hallberg EJ[2], Cogswell JA[2], Heins CN[2], Couch FJ[3], Boughey JC[4].





In caso di quad + CHT importante test prima della RT



CHIRURGIA Oncologica in CM-BRCA
Esperienza SSD Chirurgia dei Tumori Eredo-famigliari
2005-2023

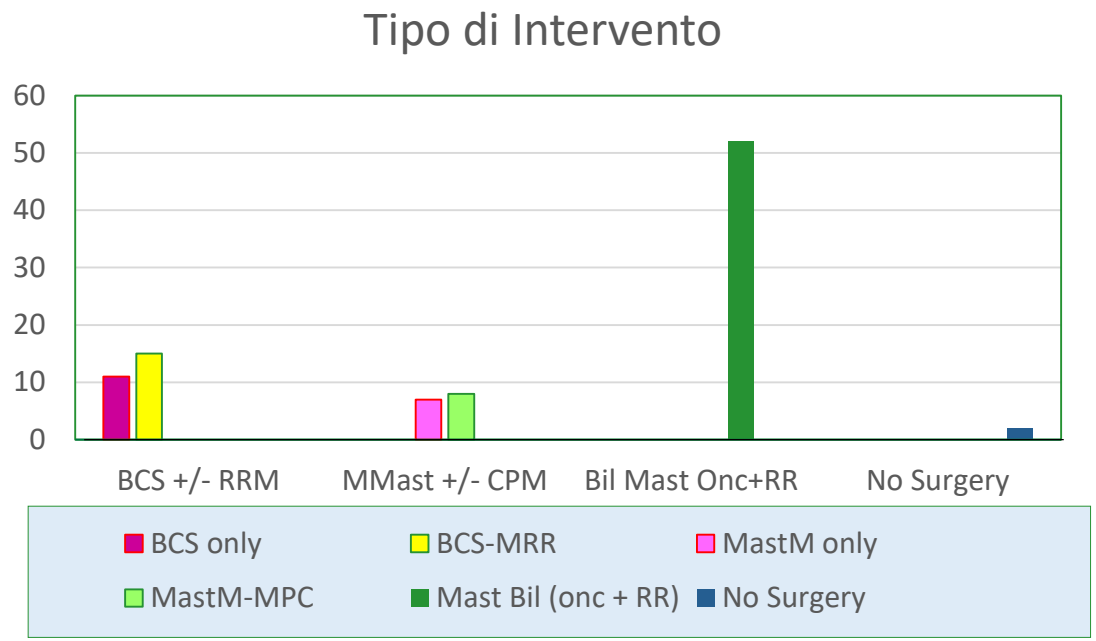
N = 96 pz

Età= 41,8 ± 10 anni (28 ÷ 77)

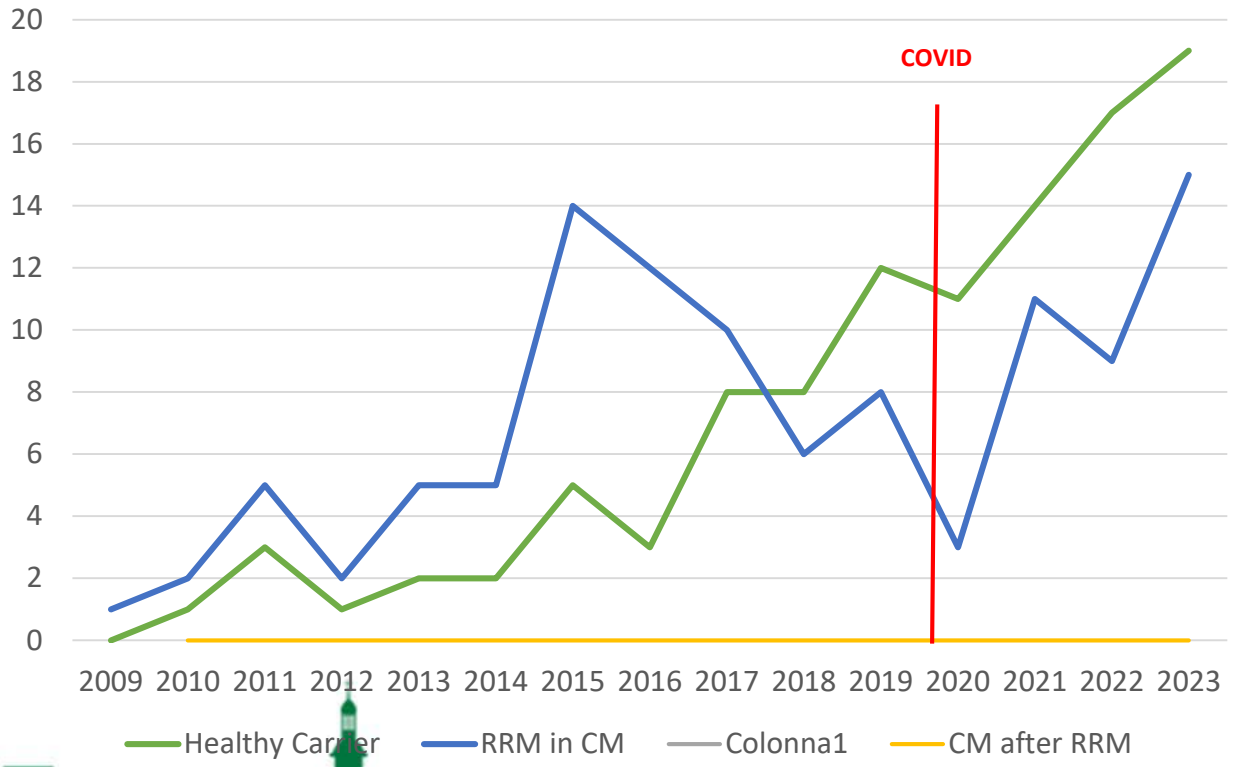
Chirurgia	N	%
Nessuna Chirurgia	2	**2,2**
BCS	11	**12,2**
BCS e successiva MRR bil	15	**15,5**
MastM (monolaterale)	7	**6,6**
MastM e successiva MPC	8	**8,8**
Mast Bilaterale (Onc + RR)	52	**56,6**
Mast Bil tot sinc / meta	73	**81,1**

* solo 3 dopo RT

81,1% ha effettuato Mastectomia Bilaterale sincrona (oncologica e RR) o metacrona



Mastectomia Profilattica (MRR)
Esperienza SSD Chirurgia dei Tumori Eredo-famigliari
2009-2023



Attività di Mastectomia Profilattica
N = 331 MRR in 208 pz

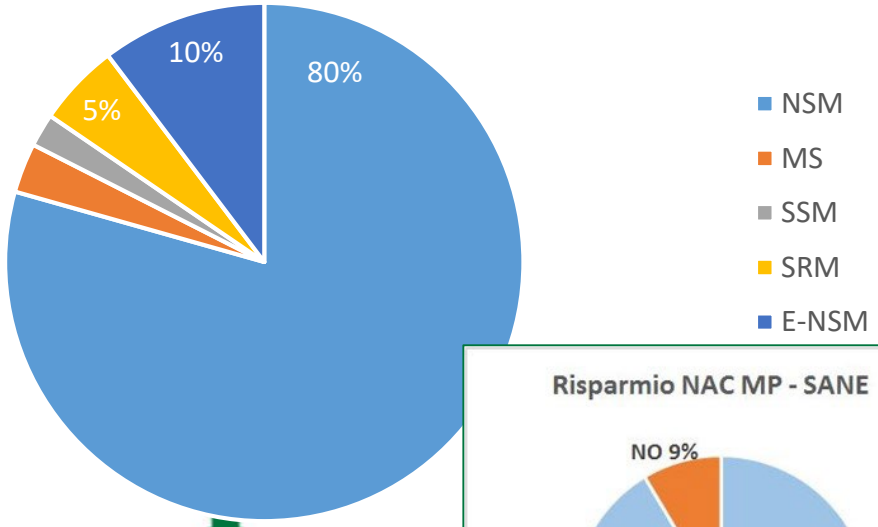
N pz CM in atto o pregresso:
114 (MRR n. 143)
N carrier sane: **94** (MRR n. 188)

TREND: inversione gruppi

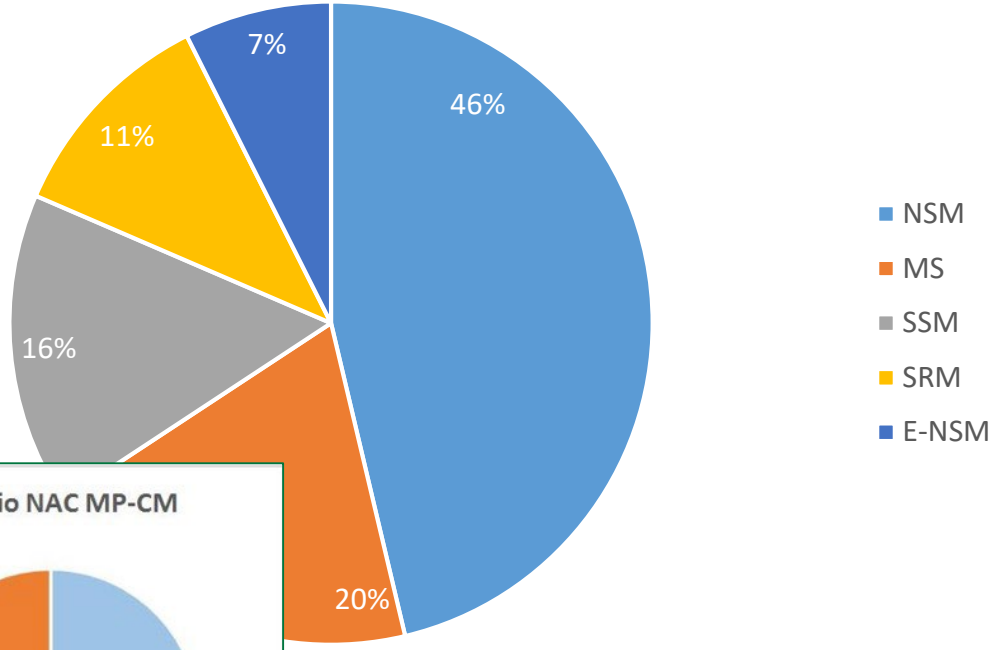
CM dopo 331 MRR: 0 dal 2009

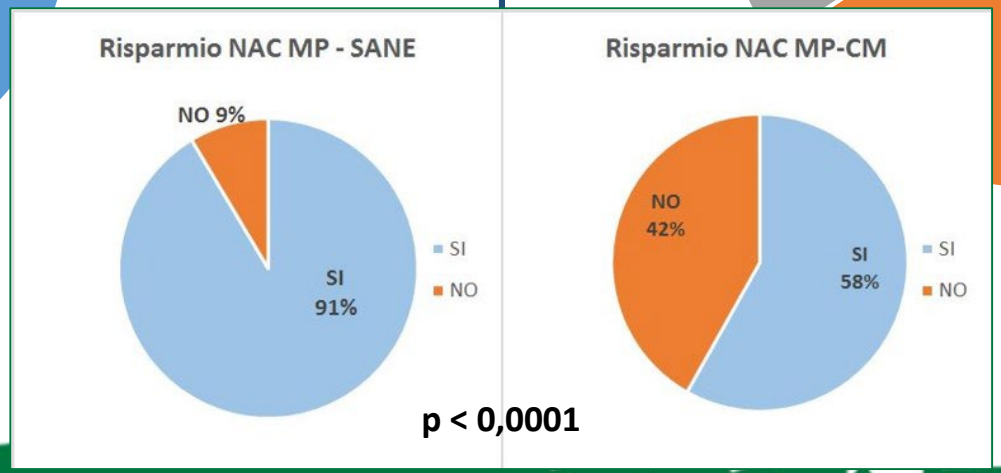
RRM: surgical technique in 207 pts (n = 339 RRM)

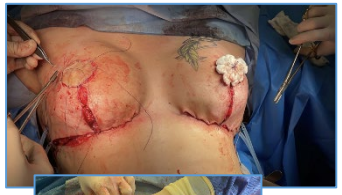
N = **99 healthy carrier BRCA**, 198 RRM

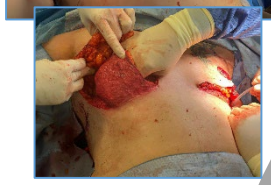


N = 112 pts with BRCA-**BC**, 141 RRM

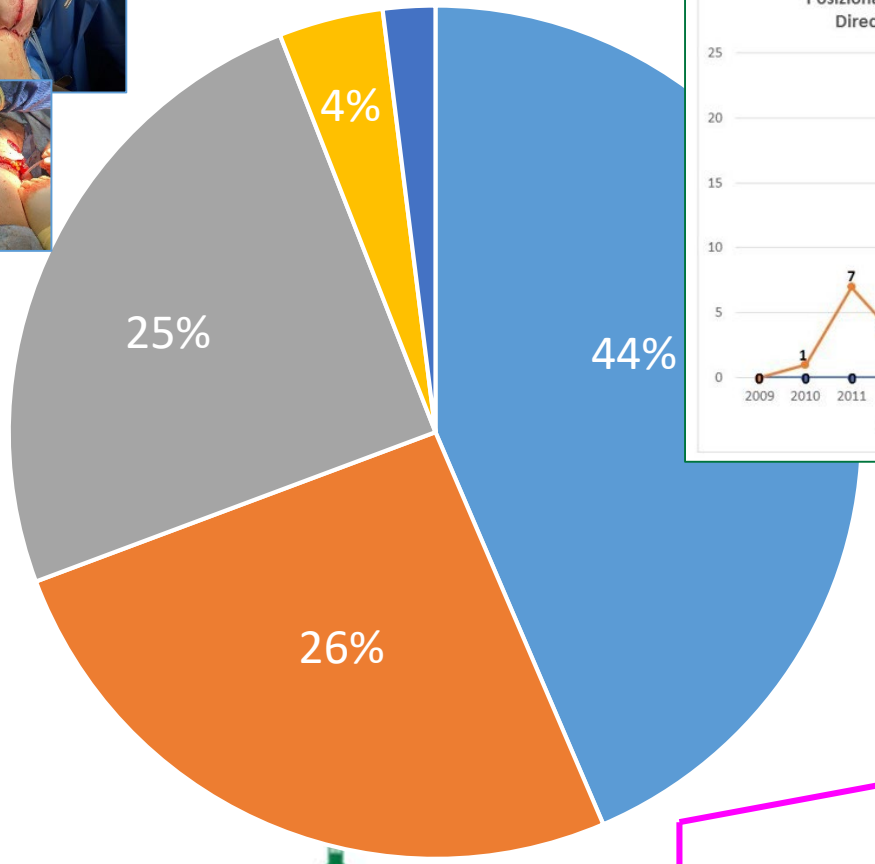




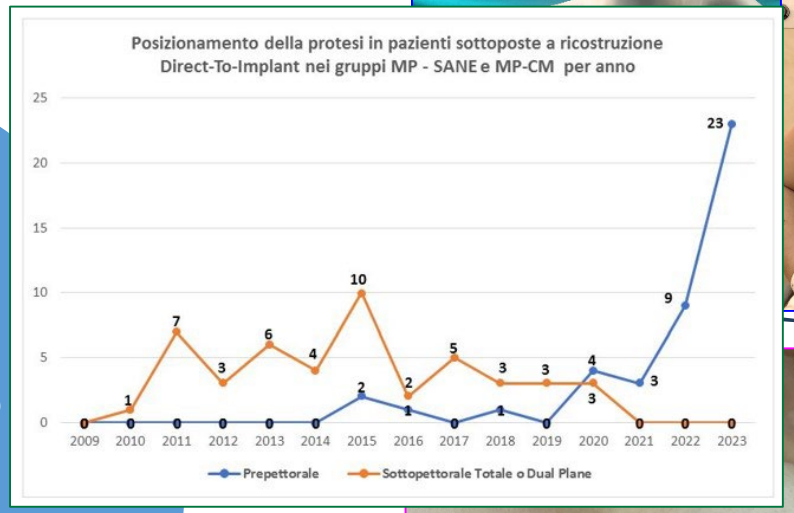


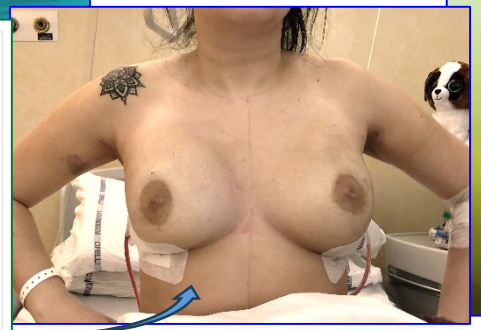


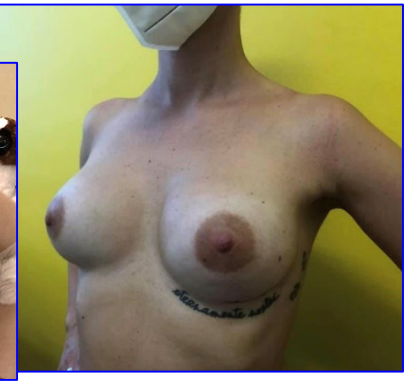
Tecnica Ricostruttiva

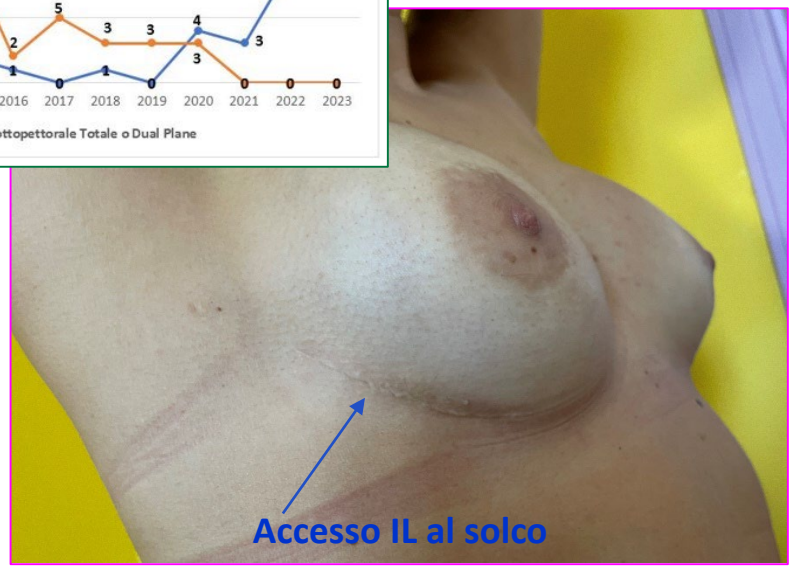


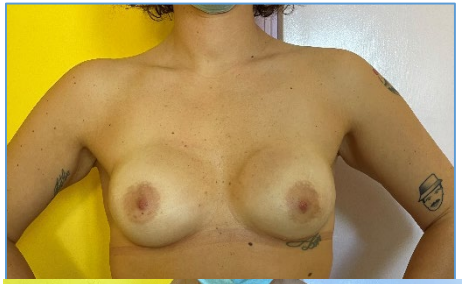
29%

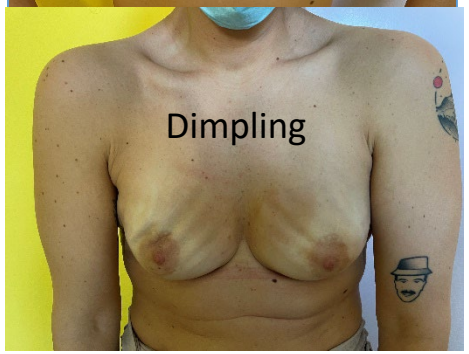












54% ricostruzione immediata definitiva

Adesione a studio prospettico I-PREPARE project di EUBREAST

Raccomandazione LG AIOM «Tumori eredo-familiari» 2024 BOZZA ….

Certezza delle prove	1.1.A. Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Nelle portatrici sane di VP a carico dei geni *BRCA1* o *BRCA2*, la mastectomia di riduzione del rischio di CM come opzione alternativa alla sorveglianza strumentale dovrebbe essere presa in considerazione, ai fini di una prevenzione primaria del CM e della mortalità associata	**Forte a favore**
COI: nessun conflitto dichiarato		

Aiom

Associazione Italiana Oncologia Medica

Gent. Profssa
Alberta Ferrari

Sua Sede

Milano, 31 marzo 2022

Oggetto: Linee Guida AIOM 2022 "Tumori eredo-familiari"

Gentilissima,

ho il piacere di comunicarLe che il Consiglio Direttivo AIOM ha accolto la proposta di ANISC di inserire il Suo nominativo fra gli estensori per la stesura delle linee guida di cui in oggetto, coordinate da Antonio Russo.

Certezza delle prove	1.1.B. Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Nelle portatrici di VP a carico dei geni *BRCA1* o *BRCA2* con CM in atto o in anamnesi, la mastectomia di riduzione del rischio di carcinoma mammario della mammella controlaterale al tumore (mastectomia controlaterale profilattica) associata alla mastectomia dal lato oncologico, in alternativa alla chirurgia conservativa e alla sorveglianza strumentale, dovrebbe essere presa in considerazione, tenendo conto dell'età della paziente, del gene coinvolto (*BRCA1* vs *BRCA2*), della prognosi del tumore già sviluppato e del trattamento adiuvante previsto o in atto.	**Forte a favore**

Terapia adiuvante: scelte differenti - perchè?

Position Paper: "Test di analisi dei profili di espressione genica nel carcinoma della mammella"

A cura del Gruppo di Lavoro AIOM – SIAPEC-IAP – SIBIOC – SIF

Giordano Beretta, Massimo Barberis, Ettore Capoluongo, Isabella Castellano, Saverio Cinieri, Laura Cortesi, Romano Danesi, Lucia Del Mastro, Marzia Del Re, Serena Di Cosimo, Stefania Gori, Lorena Incorvaia, Nicla La Verde, Giuseppe Perrone, Nicola Silvestris, Pierosandro Tagliaferri, Antonio Russo

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

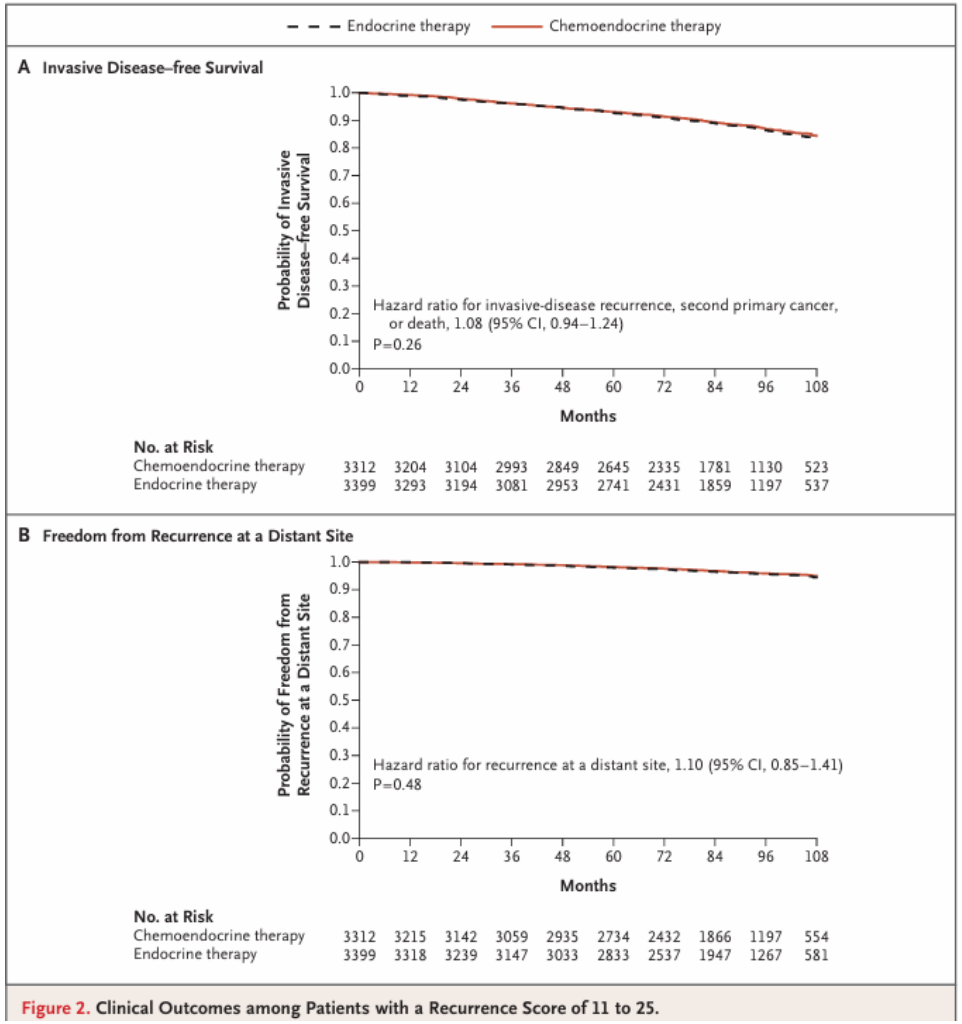


Figure 2. Clinical Outcomes among Patients with a Recurrence Score of 11 to 25.

Lucia

Decision-making senologico

Riduzione del Rischio

Elisabetta

Decision-making ginecologico

La donna e orientata ad effettuare mastectomia controlaterale RR senza ricostruzione.
Si specifica che nel suo caso individule il rischio di CM controlaterale e ridotto rispetto alla media delle persone con mutazione BRCA in funzione: dell'eta di insorgenza del primo tumore > 40 anni, di BRCA2, del trattamento ormonale in corso.
La donna prende atto di queste informazioni e si riserva di riflettere ulteriormente, facendoci sapere la sua decisione finale alla mail:
senologia.amb@smatteo.pv.it

6-02-2017

La donna ribadisce la propria decisione, gia espressa in passato, di voler effettuare una mastectomia profilattica controlaterale senza ricostruzione.
Si specifica ancora una volta che nel suo caso individule il rischio di CM controlaterale e ridotto rispetto alla media delle persone con mutazione BRCA in funzione: dell'eta di insorgenza del primo tumore > 40 anni, di BRCA2, del trattamento ormonale in corso.
La donna ha prso atto di queste informazioni e, dopo periodo di accurata riflessione, chiede di essere sottoposta a mastectomia della mammella sana a rischio moderato di tumore controlaterale.
La donna viene pertanto inserita in lista d'attesa per mastectomia semplice monolaterale sinistra di riduzione del rischio, senza ricostruzione per scelta della paziente.
Da programmare valutazione psicologica.

11-09-2017

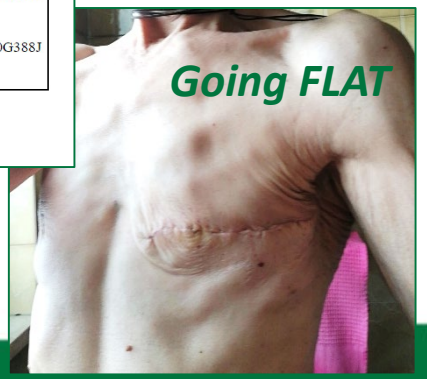
FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA
Registro Operatorio

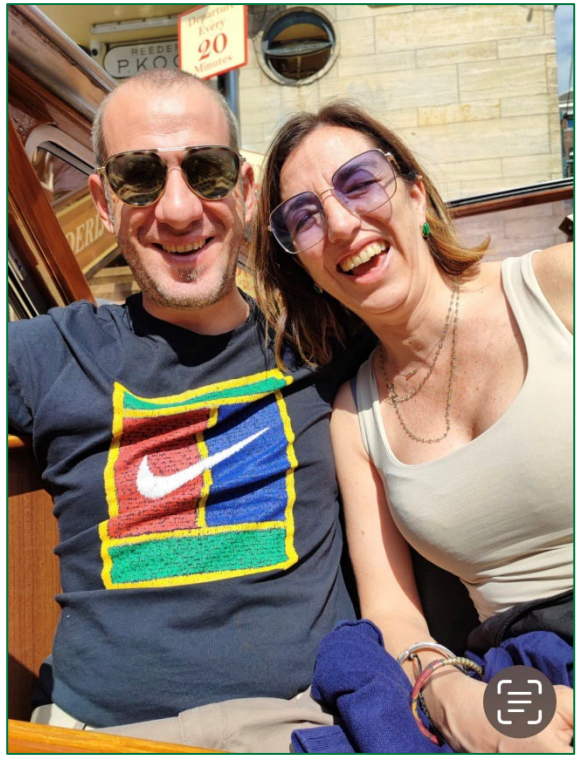
N°. Registro 431

Paziente GUERRA LUCIA MARIA ANTONIETTA **Sesso** F **Data Nascita** 10/08/1952 **Età** 65 ANNI
Blocco Op. CARDIOCHIRURGIA **Spec. Chirurgica** SENOLOGIA
Sala Op. SO1 **Data Intervento** 30/11/2017 **Nosologico** 37056088 **Codice Fiscale** GRRLMR52M50G388J
Regime di Ricovero Ordinario **Tipologia di Intervento** ELEZIONE

Diagnosi (ICD-9-CM)
V50.41 - RIMOZIONE PROFILATTICA DELLA MAMMELLA
V84.01 - SUSCETTIBILITA GENETICA AL TUMORE MALIGNO DELLA MAMMELLA

30-11-2017





26-10-2020

FONDAZIONE IRCCS POLICLINICO SAN MATTEO - PAVIA
Registro Operatorio

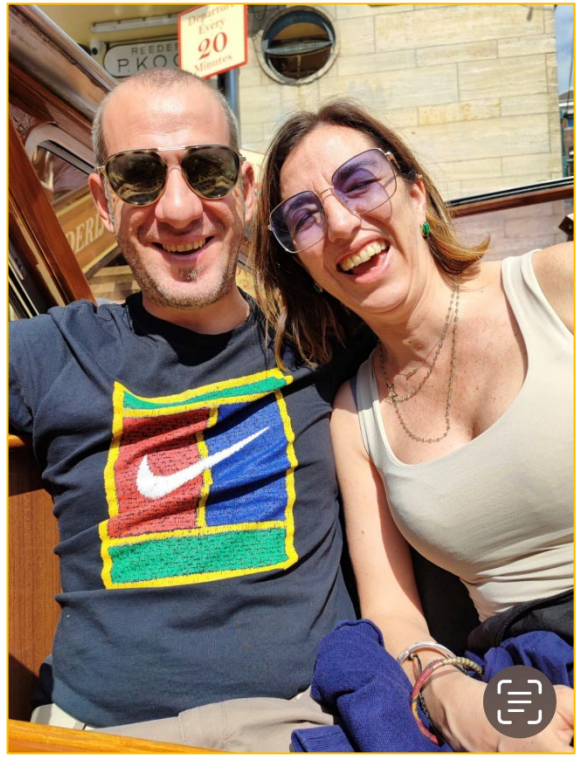
N°. Registro 488

Paziente CAPITTINI ELISABETTA **Sesso** F **Data Nascita** 10/12/1979 **Età** 40 ANNI
Blocco Op. DEA CHIR **Spec. Chirurgica** GINECOLOGIA
Sala Op. SO7 **Data Intervento** 26/10/2020 **Nosologico** 40039590 **Codice Fiscale** CPTLBT79T50F080V
Regime di Ricovero Ordinario **Tipologia di Intervento** ELEZIONE

Diagnosi (ICD-9-CM)
V50.42 - RIMOZIONE PROFILATTICA DELL'OVAIO

Diventare genitori fin dalla scoperta del tumore:

MISSION IMPOSSIBLE?



GRAND ROUNDS CLINICI DEL MERCOLEDÌ

Is it safe to interrupt adjuvant endocrine therapy to conceive? (1)

Out of 7796 screened studies, 8 were included in the final analysis

A total of 3805 patients with hormone receptor-positive invasive early breast cancer (BC) were included, of whom 1285 had a pregnancy after BC diagnosis

In 3 studies (n=987 patients), no difference was observed between patients with and those without a subsequent pregnancy (HR 0.96, 95% CI 0.75-1.24, P = 0.781)

In the 6 studies (n=3504 patients) reporting on OS, patients with a pregnancy after BC had a statistically significant better OS than those without a pregnancy (HR 0.46, 95% CI 0.27-0.77, P < 0.05)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Safety of pregnancy after breast cancer in young women with hormone receptor-positive disease: a systematic review and meta-analysis

L. Arecco[1,2†], E. Blondeaux[3†], M. Bruzzone[3], M. M. Latocca[2], E. Mariamidze[4], S. Begijanashvili[5], E. Sokolovic[6], G. Gentile[7], G. Scavone[2], S. Ottonello[2], A. Boutros[1,8], I. Vaz-Luis[9], C. Saura[10], R. A. Anderson[11], I. Demeestere[12], H. A. Azim, Jr[13], E. de Azambuja[14], F. A. Peccatori[15], L. Del Mastro[1,2], A. H. Partridge[16] & M. Lambertini[1,2*]

[1]Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova; [2]Department of Medical Oncology, U.O.C. Clinica

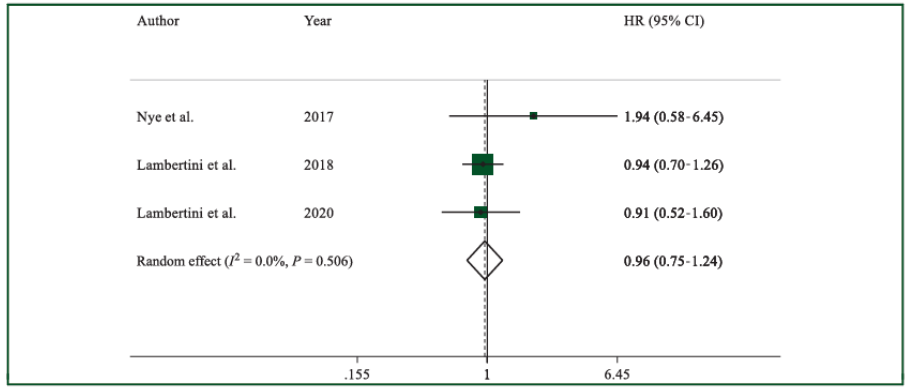


Figure 2. Forest plot describing event-free survival of patients who had a pregnancy after hormone receptor-positive breast cancer as compared to the non-pregnancy cohort.
CI, confidence interval; HR, hazard ratio.

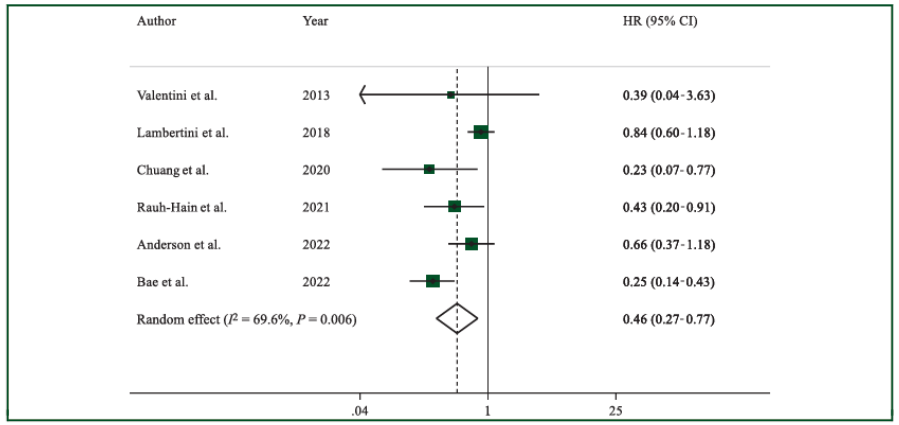


Figure 3. Forest plot describing overall survival of patients who had a pregnancy after hormone receptor-positive breast cancer as compared to the non-pregnancy cohort.
CI, confidence interval; HR, hazard ratio.

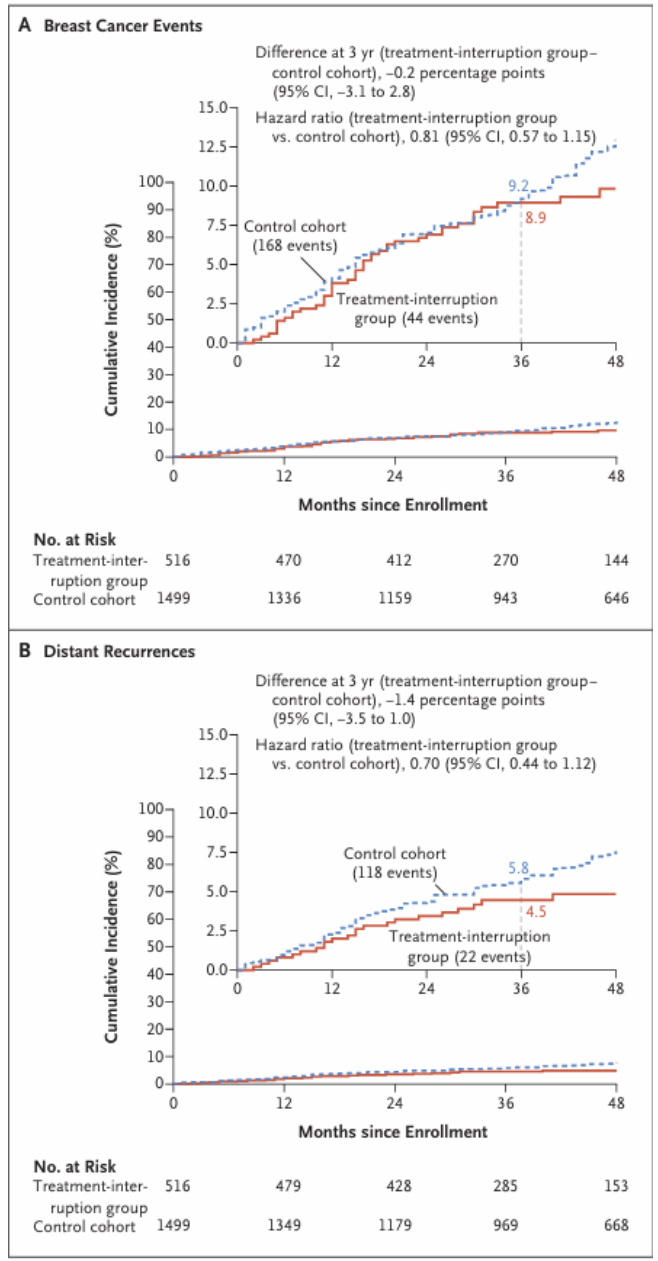
Is it safe to interrupt adjuvant endocrine therapy to conceive? (2)

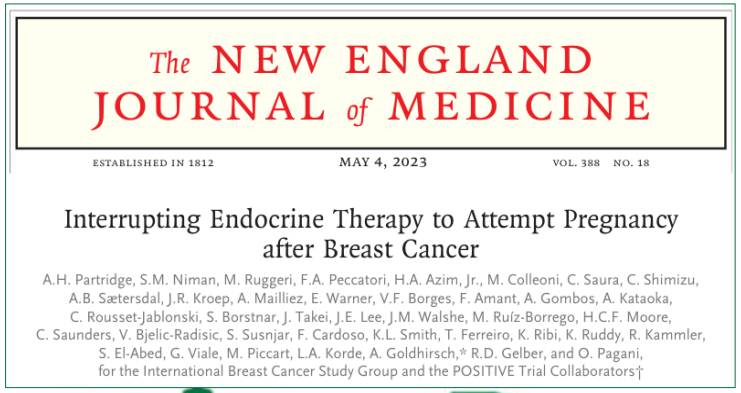
Among 516 women, the median age was 37 years, the median time from BC diagnosis to enrollment was 29 months

Among 497 women who were followed for pregnancy status, 368 (74.0%) had at least one pregnancy and 317 (63.8%) had at least one live birth

At a median follow-up, 41 months), 44 patients had a BC-event

The 3-year incidence of BC-events was 8.9% (95%CI 6.3 to 11.6) in the treatment-interruption group and 9.2% (95% CI, 7.6 to 10.8) in the control cohort





- ✓ 27/10/2015 AMH 0,1 ng/ml, AFC=4
- ✓ Novembre 2015 : tentativo pick ovocitario fallito per bassa riserva ovarica.

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

Safety of assisted reproductive techniques in young women harboring germline pathogenic variants in *BRCA*1/2 with a pregnancy after prior history of breast cancer

M. Condorelli[1,2], M. Bruzzone[3], M. Ceppi[3], A. Ferrari[4,5], A. Grinshpun[6], A. S. Hamy[7], E. de Azambuja[8], E. Carrasco[9], F. A. Peccatori[10], A. Di Meglio[11], S. Paluch-Shimon[6,12], P. D. Poorvu[13], M. Venturelli[14], C. Rousset-Jablonski[15], C. Senechal[16], L. Livraghi[17,18], R. Ponzone[19], L. De Marchis[20], K. Pogoda[21], A. Sonnenblick[22], C. Villarreal-Garza[23], O. Córdoba[24], L. Teixeira[25], F. Clatot[26], K. Punie[27], R. Graffeo[28], M. V. Dieci[29,30], J. A. Pérez-Fidalgo[31], F. P. Duhoux[32], F. Puglisi[33,34], A. R. Ferreira[35], E. Blondeaux[36], T. Peretz-Yablonski[6], O. Caron[37], C. Saule[38], L. Ameye[39], J. Balmaña[9], A. H. Partridge[13], H. A. Azim[23], I. Demeestere[1,2] & M. Lambertini[40,41*]

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.

BRCA & REDUCTION IN OVARIAN RESERVE

- ✓ Accelerated ovarian aging (Ben-Aharon I et al, 2018).
- ✓ Reduced ovarian reserve both quantitatively and qualitatively (Wang ET et al, 2014).
- ✓ Lower AMH levels at BC diagnosis (Phillips KA et al, 2016).
- ✓ Lower number of oocytes retrieved after each cycle of stimulation (Broer et al., 2013; Iliodromiti et al., 2014).

Volume 6 ■ Issue 6 ■ 2021 https://doi.org/10.1016/j.esmoop.2021.100300

- ✓ Marzo 2018: sospende LHRH analogo + Tamoxifene 20 mg (dopo 27 mesi), per desiderio di prole.
- ✓ Aprile-settembre 2018: washo-out e avvio di rapporti liberi con mancato concepimento spontaneo.
- ✓ Agosto 2019: embriotransfer di 2 blastocisti (ovodonazione), esitata in gravidanza tubarica destra, esitata in aborto tubarico spontano, con negativizzazione delle betaHCG in settembre 2019.
- ✓ Gennaio 2020: ripresa della terapia ormonale conclusa a Maggio 2022 (30 mesi)
- ✓ 26/10/2020 (40 aa): annessiectomia profilattica. EI: tube nei limiti, non evidenza di lesioni displastiche intraepiteliali (p53/Do7+ wild type; non significativo incremento dell'indice di proliferazione); washing negativo.

Article

Pathologic Findings at Risk Reducing Surgery in *BRCA* and Non-*BRCA* Mutation Carriers: A Single-Center Experience

Chiara Cassani [1], Chiara Rossi [2], Cristina Angela Camnasio [1], Mario Urtis [3], Giacomo Fiandrino [4], Maurizia Grasso [3], Francesca Zanellini [5], Marco Lucioni [2], Gioacchino D'Ambrosio [4], Alessandro Di Toro [3], Margherita Rossi [5], Marianna Roccio [5], Alberta Ferrari [6], Simona Secondino [7], Rossella Elena Nappi [8], Eloisa Arbustini [3], Marco Paulli [2], Arsenio Spinillo [1] and Stefania Cesari [4,*]

AGE FACTOR

65/81 (80.2%) BRCA1 and 37/63 BRCA2 (58.7%) underwent surgery beyond guideline recommended ages and the detection of pathologic findings on histology was significantly higher in those older than 45 (age > 45 years = 35/114 vs. age 45 years = 7/66; p = 0.0019).

Table 1. Baseline and clinical features of study population according to mutation status.

	BRCA1	*BRCA2*	Other Genes	Family Risk	Total	Controls
N (% on overall study population)	85	63	27	15	190	145
Mean age at genetic test (range)	46.9 (26–79)	48.01 (31–71)	51.29 (39–77)	47.38 (39–53)	47.94 (26–79)	–
BMI mean (range)	23.93 (17–37)	23.80 (17–38.3)	22.21 (18–32)	23.55 (18–33.6)	23.61 (17–38.3)	25.06 (15–40)
OC use (%)	33 (39.28)	30 (47.6)	9 (33.3)	6 (40)	81 (42.63)	48 (31.1)
History of BC (%)	49 (58.33)	47 (74.6)	10 (37.03)	10 (66.66)	116 (61.05)	0
Tamoxifen use(%)	16 (19.04)	27 (42.85)	4 (14.81)	5 (33.33)	52 (27.36)	0
Previous chemotherapy (%)	38 (45.23)	36 (57.14)	7 (25.92)	5 (33)	86 (45.26)	0
Parity						
0	21 (24.7)	17 (26.98)	6 (22.22)	7 (46.66)	51 (26.84)	34 (23.44)
1	19 (22.3)	17 (26.98)	9 (33.33)	1 (6.66)	46 (24.21)	43 (29.65)
≥2	45 (52.9)	29 (46.03)	12 (44.44)	7 (46.66)	93 (48.95)	68 (46.89)
Menopausal status at surgery						
Premenopause (%)	35 (41.11)	16 (25.39)	10 (37.03)	5 (33.33)	66 (34.73)	92 (63.44)
Postmenopause (%)	50 (58.82)	47 (74.60)	17 (62.96)	10 (66.66)	124 (65.26)	53 (36.55)
Relatives with OC (%)	46 (54.11)	27(42.85)	20 (74.07)	10 (66.66)	103 (54.21)	0
Relatives with BC (%)	65 (76.47)	53 (84.12)	15 (55.55)	8 (53.33)	141 (74.21)	0
Basal CA 125 U/mL mean (range)	10.47 (2–149)	8.86 (2–74)	7.02 (3.5–13.6)	8.27 (3.1– 21.8)	9.27 (2–149)	–

Diagnostics **2022**, *12*, 3054. https://doi.org/10.3390/diagnostics12123054

- ✓ 31/03/2023: Embriotransfer di 2 blastocisti (ovodonazione), esitata in gravidanza gemellare bicoriale biamniotica
- ✓ DPP 17/12/202
- ✓ 09/08/2023: OGTT 83-184*-168*, GDM in terapia dietetica, in ottimo compenso.
- ✓ 17/11/2023: taglio cesareo in urgenza a 35 + 5 wks per iniziale travaglio, primo feto in presentazione podalica
- ✓ F 2505 g , F 2155 g, EBL= 1000 ml
- ✓ Apgar 8-10 e 10-10 a 1 e 5 minuti

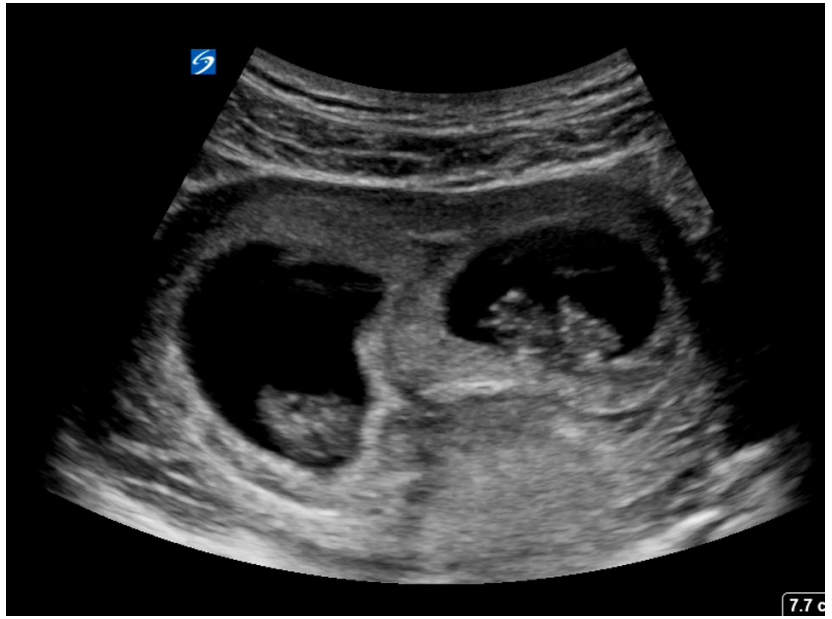


Table 2. Pregnancy, Fetal, and Obstetric Outcomes in Patients With a Pregnancy After Breast Cancer

Outcomes	No. (%) (n = 659)
Age at pregnancy, median (IQR), y	34.7 (31.8-37.3)
Time from diagnosis to conception, median (IQR) y	3.5 (2.2-5.3)
Pregnancy interval	
≤2 Years after diagnosis	131 (19.9)
Between >2 and ≤5 years after diagnosis	345 (52.4)
>5 Years after diagnosis	183 (27.8)
Type of conception	
Spontaneous pregnancy	461/582 (79.2)
Use of assisted reproductive technology	121/582 (20.8)
Embryo transfer after oocyte/embryo cryopreservation at diagnosis of breast cancer	48
Embryo transfer following oocyte donation	29
Ovarian stimulation for IVF/ICSI/ovulation induction after anticancer treatment	36
Unknown type of assisted reproductive technology	8
Pregnancy outcome	n = 649
Delivered	517 (79.7)
Ongoing pregnancy	24 (3.7)
Miscarriage	63 (9.7)
Induced abortion	45 (6.9)
No. of live births from first pregnancy after breast cancer[a]	n = 517
1	463 (89.6)
2	54 (10.4)
Timing of delivery[a]	n = 446
At term (≥37 wk)	406 (91.0)
Preterm (<37 wk)	40 (9.0)
Complications[a]	n = 471
None	365 (86.3)
Pregnancy complications	27 (6.4)
Delivery complications	22 (5.2)
Congenital abnormalities[b,c]	4 (0.9)
Fetal complications[b,c]	3 (0.6)
Other complications[b]	2 (0.5)
Breastfeeding[a]	133/403 (33.0)
Duration, median (IQR), mo	5 (2-6)
Unknown, No.	50

Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

[a] Calculated from the total number of delivered pregnancies.

[b] Calculated from the total number of infants born to patients with known information on pregnancy complications (n = 470).

[c] Congenital abnormalities included cardiac malformation (n = 2), congenital diaphragmatic hernia (n = 1), and chromosome abnormality with karyotype 47,XXY (n = 1). Fetal complications included respiratory distress (n = 2) and neonatal icterus treated with phototherapy (n = 1). Other complications included maternal internal carotid artery aneurysm (n = 1) and kidney failure in the infant due to hypoxia (n = 1).

2014 Incontro di lavoro OSM su «BRCA e gravidanza»; 2015 nascita di aBRCAdabra ETS

Pregnancy After Breast Cancer in Patients With Germline *BRCA* Mutations

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abstract

PURPOSE Young women with germline *BRCA* mutations have unique reproductive challenges. Pregnancy after breast cancer does not increase the risk of recurrence; however, very limited data are available in patients with *BRCA* mutations. This study investigated the impact of pregnancy on breast cancer outcomes in patients with germline *BRCA* mutations.

PATIENTS AND METHODS This is an international, multicenter, hospital-based, retrospective cohort study. Eligible patients were diagnosed between January 2000 and December 2012 with invasive early breast cancer at age ≤ 40 years and harbored deleterious germline *BRCA* mutations. Primary end points were pregnancy rate, and disease-free survival (DFS) between patients with and without a pregnancy after breast cancer. Pregnancy outcomes and overall survival (OS) were secondary end points. Survival analyses were adjusted for guarantee-time bias controlling for known prognostic factors.

RESULTS Of 1,252 patients with germline *BRCA* mutations (*BRCA1*, 811 patients; *BRCA2*, 430 patients; *BRCA1/2*, 11 patients) included, 195 had at least 1 pregnancy after breast cancer (pregnancy rate at 10 years, 19%; 95% CI, 17% to 22%). Induced abortions and miscarriages occurred in 16 (8.2%) and 20 (10.3%) patients, respectively. Among the 150 patients who gave birth (76.9%; 170 babies), pregnancy complications and congenital anomalies occurred in 13 (11.6%) and 2 (1.8%) cases, respectively. Median follow-up from breast cancer diagnosis was 8.3 years. No differences in DFS (adjusted hazard ratio [HR], 0.87; 95% CI, 0.61 to 1.23; $P = .41$) or OS (adjusted HR, 0.88; 95% CI, 0.50 to 1.56; $P = .66$) were observed between the pregnancy and nonpregnancy cohorts.

CONCLUSION Pregnancy after breast cancer in patients with germline *BRCA* mutations is safe without apparent worsening of maternal prognosis and is associated with favorable fetal outcomes. These results provide re-assurance to patients with *BRCA*-mutated breast cancer interested in future fertility.

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

N = 74 pz arruolate
(2000-2012, età CM ≤ 40)

- OSM
- aBRCAdabra ETS

Research

JAMA | Original Investigation

Pregnancy After Breast Cancer in Young *BRCA* Carriers
An International Hospital-Based Cohort Study

Matteo Lambertini, MD; Eva Blondeaux, MD; Elisa Agostinetto, Rinat Bernstein Molho, MD; Florentine Hilbers, PhD; Katarzyna Michail Ignatiadis, MD; Halle C. F. Moore, MD; Kelly-Anne Phillip Tiphaine Renaud, MD; Alberta Ferrari, MD; Shani Paluch-Shimo Kathryn J. Ruddy, MD; Maria Vittoria Dieci, MD; Alexios Matikas Lucia Del Mastro, MD; Fabio Puglisi, MD; Mari Luca Livraghi, MD; Florian Clatot, MD; Rinat Y Natalia Cichowska-Cwalińska, MD; Martine Be Young-Jin Lee, MD; Camille Maria, MD; Haten

...mirakova, MD; Sarah Meisel, MD; ...MD; Icro Meattini, MD; ...blick, MD; Camila Chiodi, MD; ...BCY Collaboration

DESIGN, SETTING, AND PARTICIPANTS International, multicenter, hospital-based, retrospective cohort study conducted at 78 participating centers worldwide. The study included female participants diagnosed with invasive breast cancer at age 40 years or younger between January 2000 and December 2020 carrying germline pathogenic variants in *BRCA1* and/or *BRCA2*. Last delivery was October 7, 2022; last follow-up was February 20, 2023.

CONCLUSIONS AND RELEVANCE In this global study, 1 in 5 young *BRCA* carriers conceived within 10 years after breast cancer diagnosis. Pregnancy following breast cancer in *BRCA* carriers was not associated with decreased disease-free survival.

N = 135 (74 + 61) **pz arruolate**
(2000-2012, età CM ≤ 40)

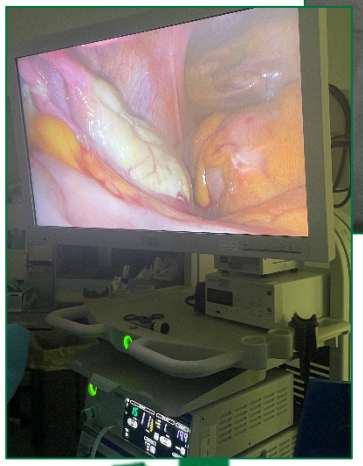
- OSM
- aBRCAdabra ETS

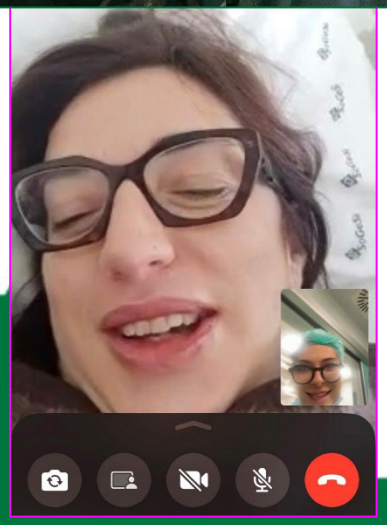
10 POSITIVE ASPECTS

N°	Description
1	The audit team appreciate the continuing positive attitude from all participants of the Breast Cancer Team.
2	The audit team appreciate the high level of research activity also maintained in 2023
3	The audit team appreciate the new project (es: HBOC Unit) and the advanced studies of BRCA variations.

BCC Certification, EUSOMA 2024

GRAND ROUNDS CLINICI DEL MERCOLEDÌ



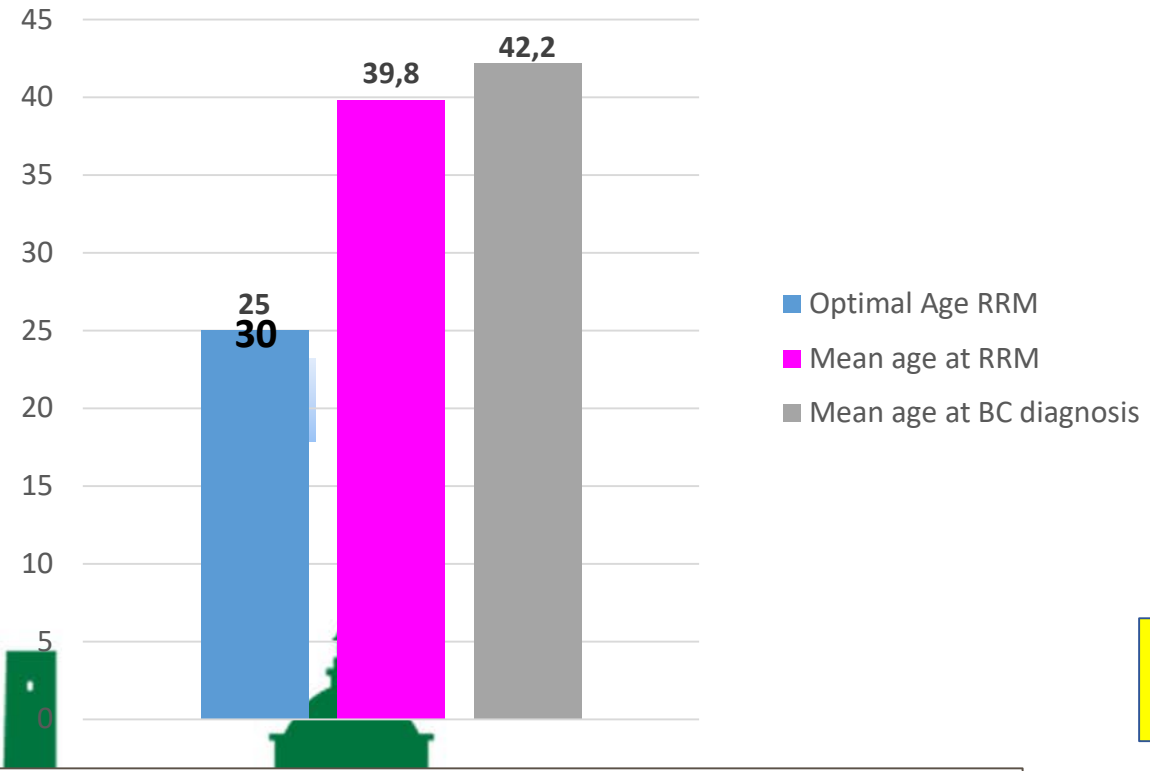


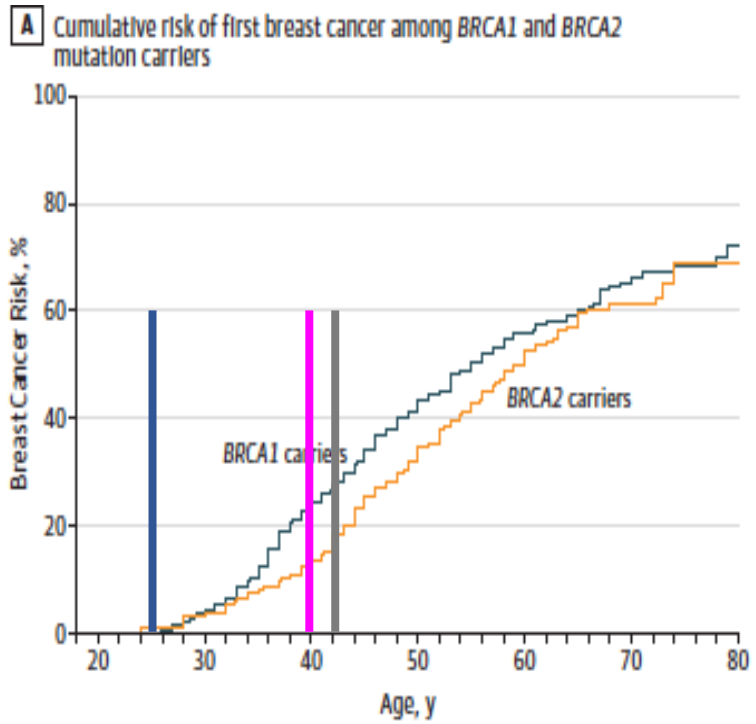
GRAND ROUNDS CLINICI DEL MERCOLEDÌ

STOP!

RRM: at what age?

MRR: Optimal age* vs Real age





In 89.4% of 296 BC-BRCA cases the genetic test was performed only after cancer diagnosis.

* Breast Cancer Res Treat. 2018 Jan;167(1):263-267. doi: 10.1007/s10549-017-4476-1. Epub 2017 Sep 15.

The expected benefit of preventive mastectomy on breast cancer incidence and mortality in BRCA mutation carriers, by age at mastectomy.

Giannakeas V[1], Narod SA[2,3].

CONCLUSIONS: Among BRCA mutation carriers, the mortality benefit of preventive mastectomy at age 25 is substantial, but the expected benefit declines rapidly with increasing age at surgery.

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM® DECEMBER 5–9, 2023 HENRY B. GONZALEZ CONVENTION CENTER SAN ANTONIO, TEXAS

Optimal age versus real age in breast and gynecological risk reducing surgery In BRCA1/2 carriers

Alberta Ferrari[§&°], Chiara Cassani[°&^], Francesca Doyle[*], Chiara Annunziata Pasqualina Anghelone[§&], Angelica Della Valle[§], Margherita Rossi[^], Gianpiero Rizzo[ϕ], Elisa Ferraris, Vincenza Praticò[§], Maria Campanella[*], Adele Sgarella[§°]

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RESULTS

This study includes **542 women**: **61.7%** were carriers of **PV in BRCA1** gene, **37.6%** of **PV in BRCA2 gene** and **0.7% in both genes** (Fig.1).

- 99 healthy carriers underwent **RRM** at the **mean age of 39.8** years (22 ÷ 60) with no difference between BRCA1 and BRCA2 carriers. Within the 296 patients with BC associated with BRCA PV (**BC-BRCA**) the mean age at disease onset was **40.9 years** (19 ÷ 78) (Fig.2). **Occult BC** at the time of RRM was detected in **2%** of cases (n=5) **among healthy carriers**, specifically 2 in situ BC and 3 invasive BC, and in **3% of cases** (n=9) **in patients with BC-BRCA:** 4 in situ BC, 3 invasive BC and 2 not specified (Fig.3). Positive family history for BC was significantly associated with the choice of RRM (p=0,006).
- 276 women underwent **RRSO**: the mean age in BRCA1 carriers was **47 years** (95%CI 45,48-48,67) and in BRCA2 carriers was **49,2 years** (95%CI 47,29-51,27). The mean age at diagnosis of OC associated with BRCA PV (**OC-BRCA**) (n=95) was **50.8 years** (95%CI 47.84-53.85) in BRCA1 (n=63) and **58.5 years** (95%CI 55,41-61,68) years in BRCA2 (n= 32) (Fig.4). **Occult OC** at the time of RRSO was detected in **7.2% of cases** (n=16) (Fig.5). Logistic regression model demonstrated that being postmenopausal (OR=8,2582; 95%CI 2,34-29,11) and parity (OR=7,81;95%CI 2,16-28,13) significantly predicted the choice of RRSO.