Con il Patrocinio di

AIOM
Associazione Italiana di Oncologia Medica

IRCCS Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

ESMO
Designated Centers of Integrated Oncology and Palliative Care

9ª edizione

Progetto **CANOA**

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2019?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Gruppo B
Coordinatori: Laura Cortesi, Ivan Moschetti

QUESITO CLINICO 2: Nelle pazienti con early breast cancer BRCA mutate, è opportuno considerare una mastectomia profilattica contro laterale?

Quale impatto nella pratica clinica?

- Valentina Sini -

Indicazioni alla CONSULENZA GENETICA e TEST BRCA

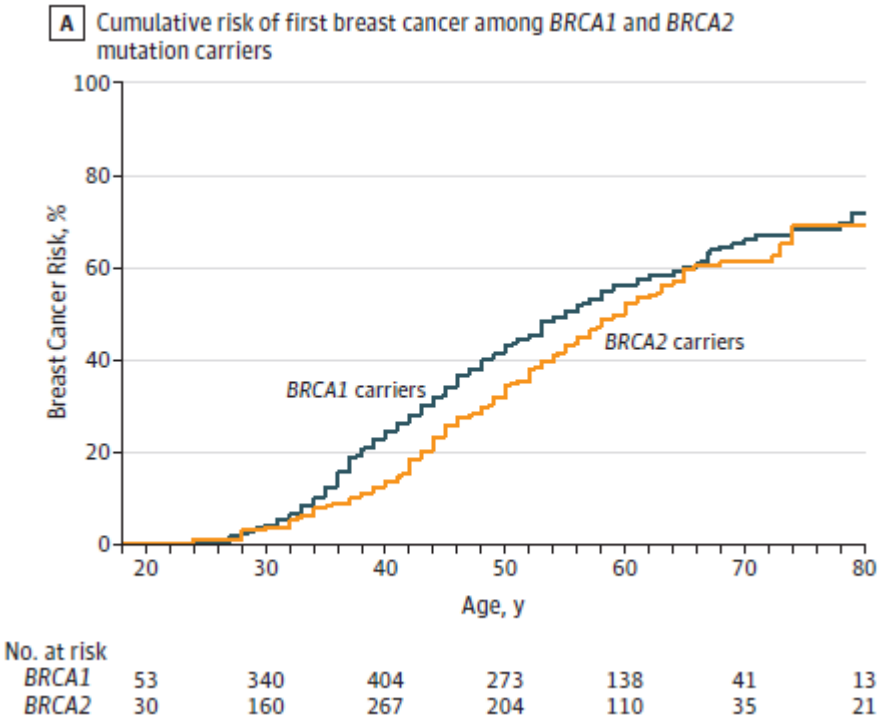
Criteri per l'invio alla consulenza genetica oncologica

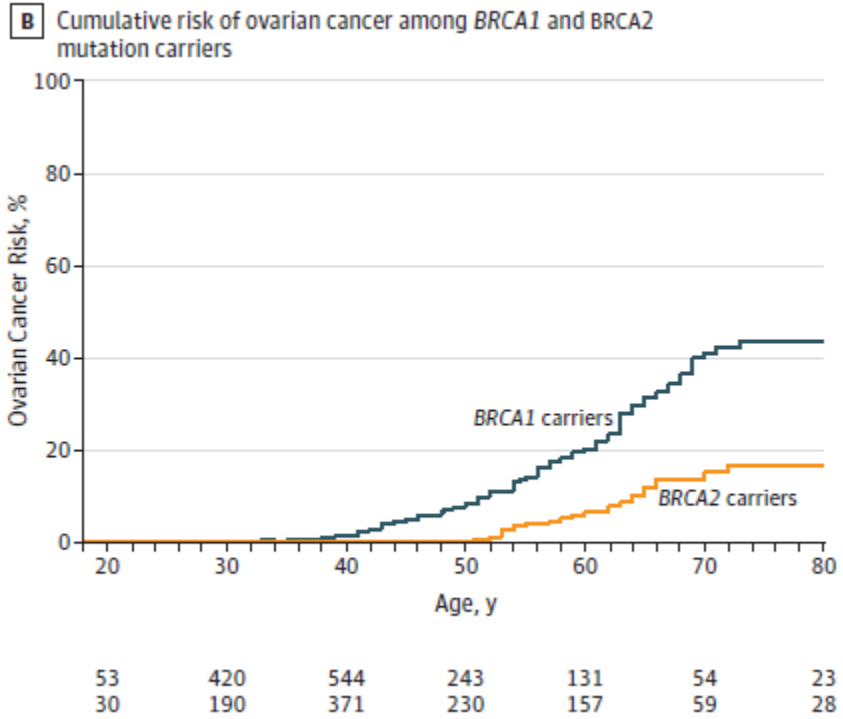
Si ritiene opportuno inviare alla consulenza genetica oncologica la donna che presenti almeno uno dei seguenti criteri[7-]:
Storia personale o familiare* di:

1. Mutazione nota in un gene predisponente (*BRCA1*, *BRCA2*, *P53*, *PTEN*, ecc.);
2. Maschio con carcinoma mammario;
3. Donna con carcinoma mammario e carcinoma ovarico;
4. Donna con carcinoma mammario < 36 anni;
5. Donna con carcinoma mammario triplo negativo < 60 anni;
6. Donna con carcinoma ovarico sieroso di alto grado a qualsiasi età;
7. Donna con carcinoma mammario bilaterale < 50 anni;
8. Donna con carcinoma mammario < 50 anni e almento 1 parente di primo grado con:
   - Carcinoma mammario < 50 anni;
   - Carcinoma ovarico non mucinoso o borderline a qualsiasi età;
   - Carcinoma mammario bilaterale;
   - Carcinoma mammario maschile;
9. Donna con carcinoma mammario > 50 anni e storia familiare di carcinoma mammario o ovarico in 2 o più parenti in primo grado* tra loro (di cui uno in primo grado con lei*).
10. Donna con carcinoma ovarico e almeno un parente di primo grado* con:
    - Carcinoma mammario < 50 anni;
    - Carcinoma ovarico a qualsiasi età;
    - Carcinoma mammario bilaterale;
    - Carcinoma mammario maschile.

**Presenza di un familiare di primo grado (genitore, fratello/sorella, figlio/a) con le caratteristiche di malattia specificate. Per il lato paterno della famiglia, considerare anche familiari di secondo grado (nonna, zie).*

Stima del RISCHIO

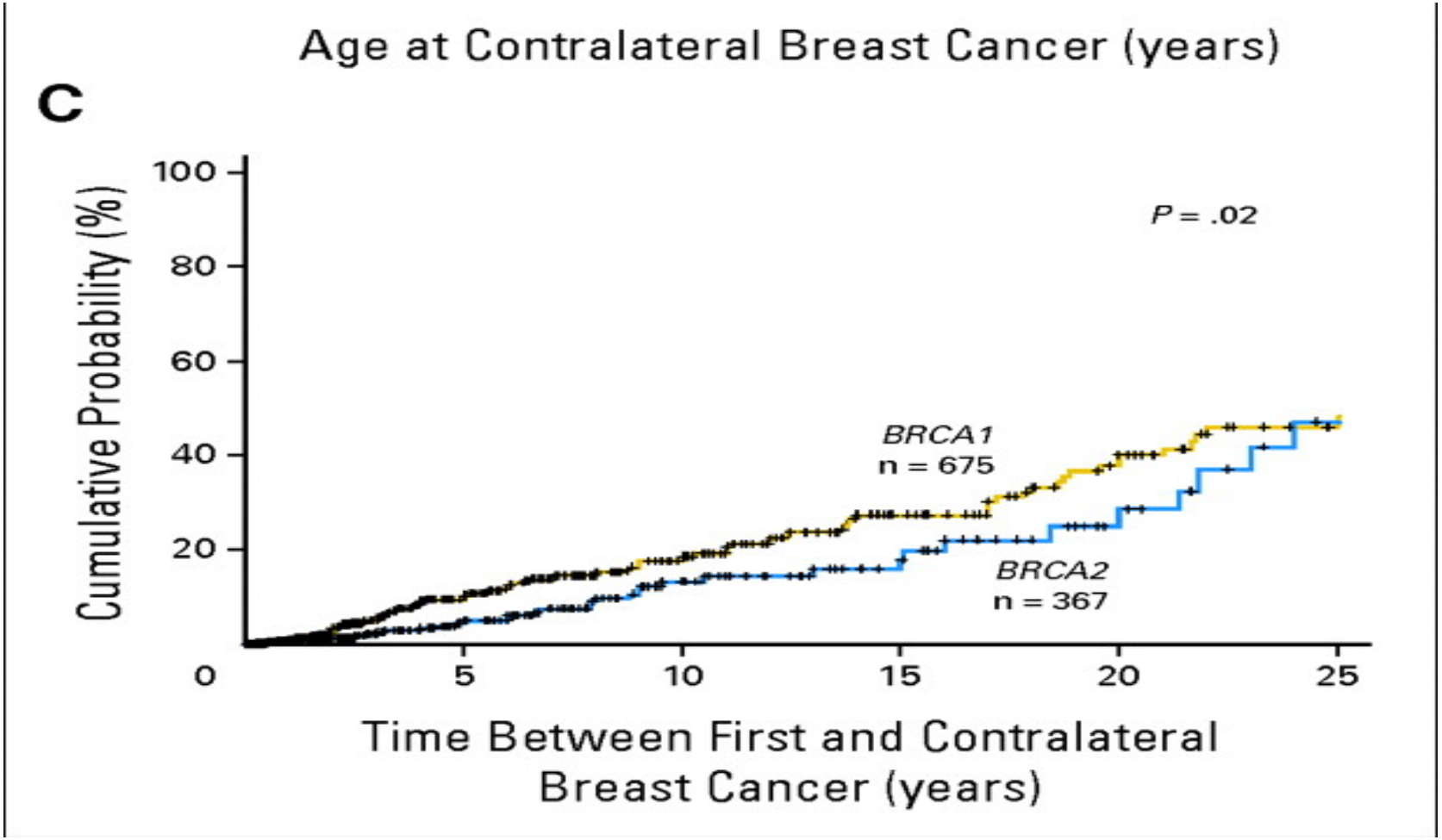




About **70%** of women who inherit a harmful BRCA1-2 mutation will develop breast cancer by the age of 80

About **44%** of women with BRCA1 mutations and about **17%** of women whith BRCA2 mutations will develop ovarian cancer by the age of 80

Rischio Cumulativo di NEOPLASIA MAMMARIA CONTROLATERALE in pazienti BRCA 1/2 MUT



The cumulative risk of contralateral breast cancer 15-20 years after the first was **40%** for BRCA1 mutation carriers and **26%** for BRCA2 mutation carriers

Graeser et al. J Clin Oncol 2009

Rischio Cumulativo di NEOPLASIA MAMMARIA CONTROLATERALE in pazienti BRCA 1/2 MUT

Table 3. Contralateral Breast Cancer Incidence Rates Per 1000 Person-Years and Kaplan-Meier Estimates of the Cumulative Risks of Contralateral Breast Cancer by Time Since First Breast Cancer, Overall and Stratified by Age at First Breast Cancer

Years Since First Breast Cancer Diagnosis	No. of Women Contributing in Category	No. of Person-Years	No. of Events	Incidence Rate per 1000 Person-Years (95% CI)	Cumulative Risk, % (95% CI)
BRCA1					
≤5	827	2107	60	28.5 (22.1-36.7)	13 (10-16)
>5-10	618	2071	53	25.6 (19.6-33.5)	23 (20-27)
>10-15	435	1438	33	22.9 (16.3-32.3)	32 (28-36)
>15-20	236	675	17	25.2 (15.7-40.5)	40 (35-45)
>20-45	132	661	10	15.1 (8.1-28.1)	53 (44-62)
BRCA2					
≤5	565	1468	27	18.4 (12.6-26.8)	8 (6-12)
>5-10	476	1543	26	16.9 (11.5-24.8)	16 (12-21)
>10-15	285	880	11	12.5 (6.9-22.6)	21 (17-26)
>15-20	138	355	5	14.1 (5.9-33.8)	26 (20-33)
>20-43	68	290	3	10.3 (3.3-32.1)	65 (25-98)

Kuchenbaecker KB et al. JAMA 2017

Chirurgia profilattica nelle portatrici di mutazione BRCA ½

- Obiettivo dell'intervento-

	Breast Cancer RR	Ovarian Cancer RR	All-Cause Mortality RR
Prophylactic bilateral mastectomy	-90%	-	ns
Prophylactic bilateral salpingo-oophorectomy	-50%	-80%	-70/80%

[1] Xiao Li, et al. Clin Cancer Res; 22(15) August 1, 2016
[2] Rebbeck, et al. J Natl Cancer Inst 2009; [3] Finch, et al. J Clin Oncol 2014;32:1547–155

Prophylactic mastectomy for the prevention of breast cancer: Review of the literature

Rawan K. Alaofi, Mohammed O. Nassif[1], Marwan R. Al-Hajeili[2]

Taibah University College of Medicine, Medina, Departments of [1]Surgery and [2]Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Table 1: Risk of developing breast cancer

BRCA genetic mutations	Cumulative risk by age 70 years (%)
BRCA1	65
BRCA2	45
Other genetic mutations	Absolute lifetime risk (%)
p53	24
PTEN	25
Histologic risk factors	10 years risk (%)
ADH	17.3
ALH	20.7
LCIS	23.7
Severe ADH	26.0
Other factors	Overall risk
Early thoracic radiation	56.7-fold
Prior history of breast cancer	5-fold

BRCA: Breast cancer, BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, PTEN: Phosphatase and tensin homolog, ADH: Atypical ductal hyperplasia, ALH: Atypical lobular hyperplasia, LCIS: Lobular carcinoma *in situ*

Table 6: Studies reporting the impact of contralateral mastectomy

Study (author, year)	Population	Main findings
Metcalfe, 2004[97]	BRCA1/2	Decreased occurrence of CBC after PM (HR=0.03; *P*=0.0005)
van Sprundel, 2005[96]	BRCA1/2	Decreased occurrence of CBC after PM (*P*<0.001)
Manning, 2015[44]	BRCA1/2	No newly diagnosed breast cancers
Peralta, 2000[98]	Unilateral BC	Decreased occurrence of CBC after PM (*P*=0.005)
Herrinton, 2005[99]	Unilateral BC	Decreased occurrence of CBC after CPM (HR=0.03; 95% CI=0.006-0.13)
Boughey, 2010[100]	Stage I or II BC and family history	95% decreased risk of CBC (HR=0.05; 95% CI=0.01-0.22; *P*<0.0001)
Babiera, 1997[101]	IFLC	No significant difference in DFS between mastectomy and conservation (*P*=0.98)

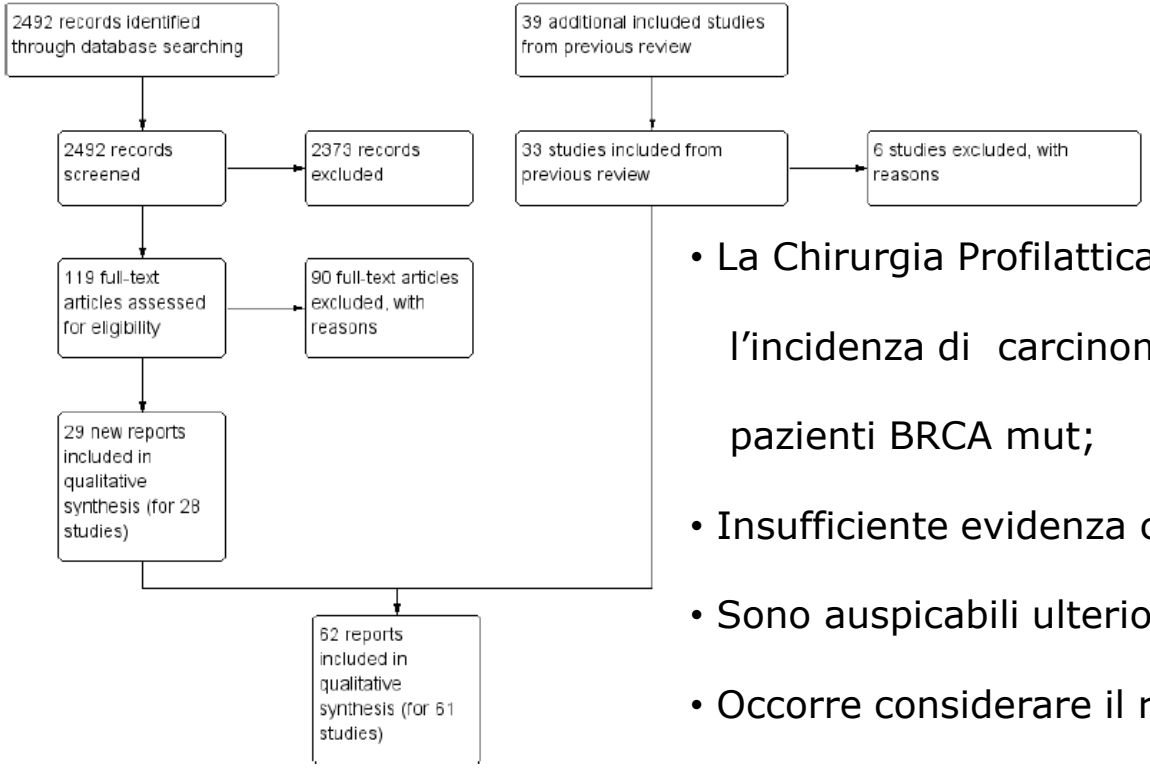
BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, CBC: Contralateral breast cancer, PM: Prophylactic mastectomy, HR: Hazard ratio, BC: Breast cancer, CPM: Contralateral prophylactic mastectomy, CI: Confidence interval, IFLC: Infiltrating lobular carcinoma, DFS: Disease free survival

Cochrane Library

Cochrane Database of Systematic Reviews

Risk-reducing mastectomy for the prevention of primary breast cancer (Review)

Carbine NE, Lostumbo L, Wallace J, Ko H



- La Chirurgia Profilattica Controlaterale (CPM) riduce l'incidenza di carcinoma mammario controlaterale in pazienti BRCA mut;
- Insufficiente evidenza circa un beneficio in sopravvivenza;
- Sono auspicabili ulteriori studi;
- Occorre considerare il rischio di ciascuna donna prima di considerare tale chirurgia;
- Considerare anche altre opzioni quali sorveglianza attiva e chemioprevenzione.

Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD002748. DOI: 10.1002/14651858.CD002748.pub4.

VOLUME 22 · NUMBER 12 · JUNE 15 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Contralateral Breast Cancer in *BRCA1* and *BRCA2* Mutation Carriers

Kelly Metcalfe, Henry T. Lynch, Parviz Ghadirian, Nadine Tung, Ivo Olivotto, Ellen Warner, Olufunmilayo I. Olopade, Andrea Eisen, Barbara Weber, Jane McLennan, Ping Sun, William D. Foulkes, and Steven A. Narod

Here we present data from a large-scale prospective study designed to generate estimates of the risk of contralateral breast cancer among women with *BRCA1* or *BRCA2* mutations, and to identify host- and treatment-related factors that might modify the risk.

1139 ≤ 65 yEBC-BRCA1/2

Stage I-II

Dx 1975-2000

638 were excluded for different reasons (dx year, not BRCA carriers, no medical informations, stage>II)

(92 were deceased at the analysis time)

327 BRCA1

152 BRCA2

9 Bilateral at DX

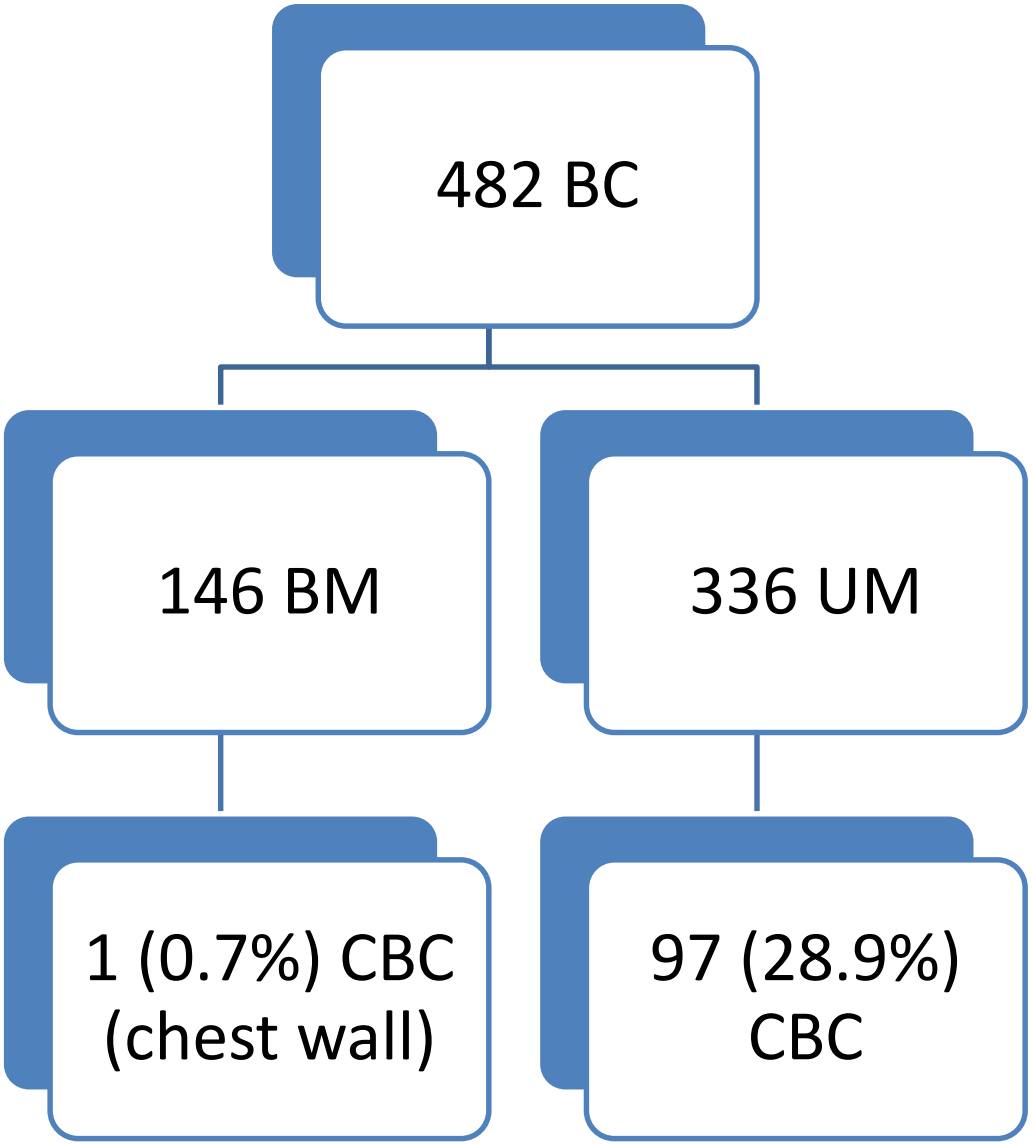
(7 BM and 2 BQ)

106 (21.9%) CPM after DX

3 CPM before DX

146 BM

Results after mFU=9.2 y



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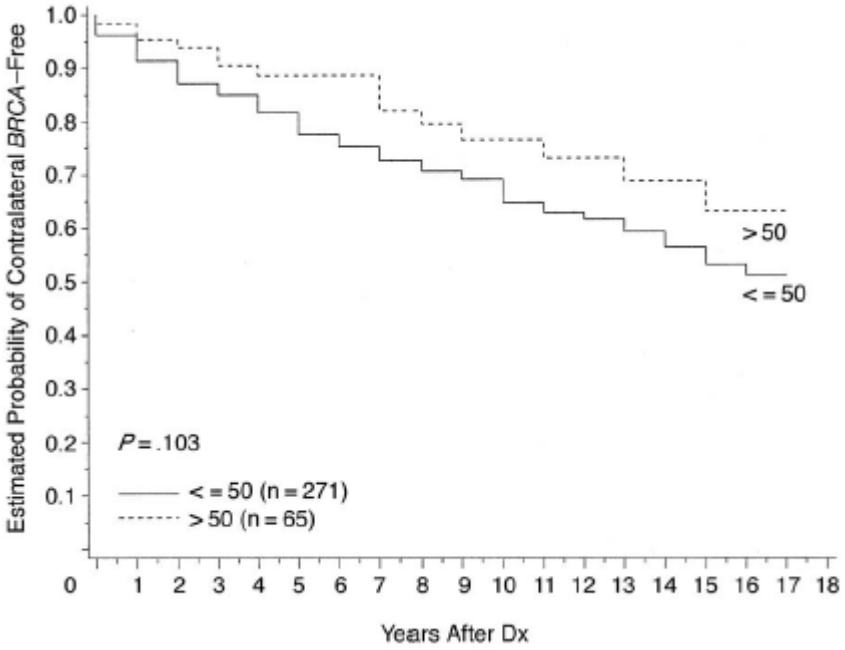

Fig 2. Actuarial risks of contralateral breast cancer in *BRCA* carriers diagnosed prior to or after age 50 years. Dx, diagnosis.

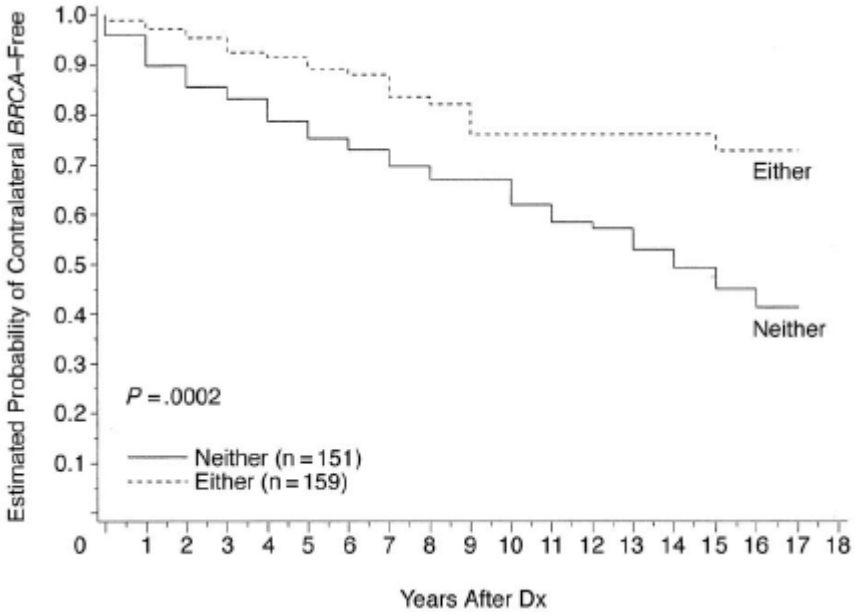

Fig 3. Actuarial risks of contralateral breast cancer in *BRCA* carriers with either tamoxifen or oophorectomy, compared with carriers receiving neither treatment. Dx, diagnosis.

Mean age at death: **48.0 years**; range, 31.5 to 84.1 years

Major cause of death: **breast or ovarian cancer**

Only **contralateral invasive** breast cancers

No woman was diagnosed with contralateral breast cancer after she was diagnosed with distal metastases.

Kelly Metcalfe et al., Journal of Clinical Oncology 2004 222328-2335

Table 4. Risks of Contralateral Breast Cancer Associated With Selected Factors

Factor	Univariate HR	Univariate 95% CI	Univariate *P*	Multivariate HR	Multivariate 95% CI	Multivariate *P*
BRCA		0.47 to 1.15	.17		0.39 to 1.09	.10
BRCA1	1.0			1.0		
BRCA2	0.73			0.65		
Age, years		0.36 to 1.10	.11		0.45 to 1.51	.52
< 50	1.0			1.0		
> 50	0.63			0.82		
Oophorectomy		0.21 to 0.91	.03		0.18 to 0.90	.03
No	1.0			1.0		
Yes	0.44			0.41		
Chemotherapy		0.68 to 1.55	.90		0.68 to 1.70	.74
No	1.0			1.0		
Yes	1.03			1.08		
Radiotherapy		0.51 to 1.16	.21		0.56 to 1.34	.51
No	1.0			1.0		
Yes	0.77			0.86		
Tamoxifen		0.35 to 1.01	.05		0.34 to 1.14	.12
No	1.0			1.0		
Yes	0.59			0.62		

NOTE. Multivariate estimates are adjusted for age, mutation (*BRCA1* or *BRCA2*), and other treatments. Analyses restricted to 336 women with intact contralateral breast.
Abbreviation: HR, hazard ratio.

Kelly Metcalfe et al., Journal of Clinical Oncology 2004 222328-2335

Table 5. Risks of Contralateral Breast Cancer Associated With Selected Factors (*BRCA1* carriers)

	Univariate			Multivariate		
Factor	HR	95% CI	*P*	HR	95% CI	*P*
Age, years		0.33 to 1.35	.25		0.44 to 1.94	.83
< 50	1.0			1.0		
> 50	0.66			0.92		
Oophorectomy		0.16 to 0.86	.021		0.13 to 0.84	.020
No	1.0			1.0		
Yes	0.37			0.33		
Chemotherapy		0.60 to 1.62	.96		0.61 to 1.76	.89
No	1.0			1.0		
Yes	0.99			1.04		
Radiotherapy		0.56 to 1.50	.74		0.59 to 1.62	.98
No	1.0			1.0		
Yes	0.92			0.98		
Tamoxifen		0.26 to 1.27	.17		0.26 to 1.33	.59
No	1.0			1.0		
Yes	0.57			0.59		

NOTE. Multivariate estimates are adjusted for age, mutation, and other treatments. Analyses restricted to 224 women with an intact contralateral breast.
Abbreviation: HR, hazard ratio.

Table 6. Risks of Contralateral Breast Cancer Associated With Selected Factors (*BRCA2* carriers)

	Univariate			Multivariate		
Factor	HR	95% CI	*P*	HR	95% CI	*P*
Age, years		0.27 to 1.66	.38		0.22 to 1.93	.45
< 50	1.0			1.0		
> 50	0.67			0.66		
Oophorectomy		0.13 to 2.45	.47		0.16 to 3.48	.72
No	1.0			1.0		
Yes	0.58			0.75		
Chemotherapy		0.51 to 2.34	.81		0.45 to 3.08	.75
No	1.0			1.0		
Yes	1.10			1.17		
Radiotherapy		0.22 to 1.04	.06		0.23 to 1.44	.24
No	1.0			1.0		
Yes	0.47			0.58		
Tamoxifen		0.33 to 1.65	.45		0.25 to 1.70	.37
No	1.0			1.0		
Yes	0.73			0.65		

NOTE. Multivariate estimates are adjusted for age, mutation, and other treatments. Analyses restricted to 112 women with an intact contralateral breast.
Abbreviation: HR, hazard ratio.

Kelly Metcalfe et al., Journal of Clinical Oncology 2004 222328-2335

VOLUME 22 · NUMBER 12 · JUNE 15 2004

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In this scenario, the risk of contralateral breast cancer is approximately 4% per year, or 40% at 10 years. The risk of contralateral cancer is almost zero for women who undergo bilateral mastectomy, and is decreased for women who undergo oophorectomy or are treated with tamoxifen.

Kelly Metcalfe et al., Journal of Clinical Oncology 2004 222328-2335

SORVEGLIANZA INTENSIVA in donne sane portatrici mutazione BRCA

Metodica	Frequenza	Inizio
Ecografia mammaria	Ogni 6 mesi	Dal momento della detection della mutazione
Rx-mammografia bilaterale	Ogni 12 mesi	Dai 35 anni fino ai 69 anni (poi ogni 24 mesi)
RM mammaria bilaterale	Ogni 12 mesi	Dall'età di 25 anni
Ecografia transvaginale+ Ca-125	Ogni 6 mesi	Dall'età di 30 anni

Modif. da Linea Guida AIOM Neoplasie mammarie -2018

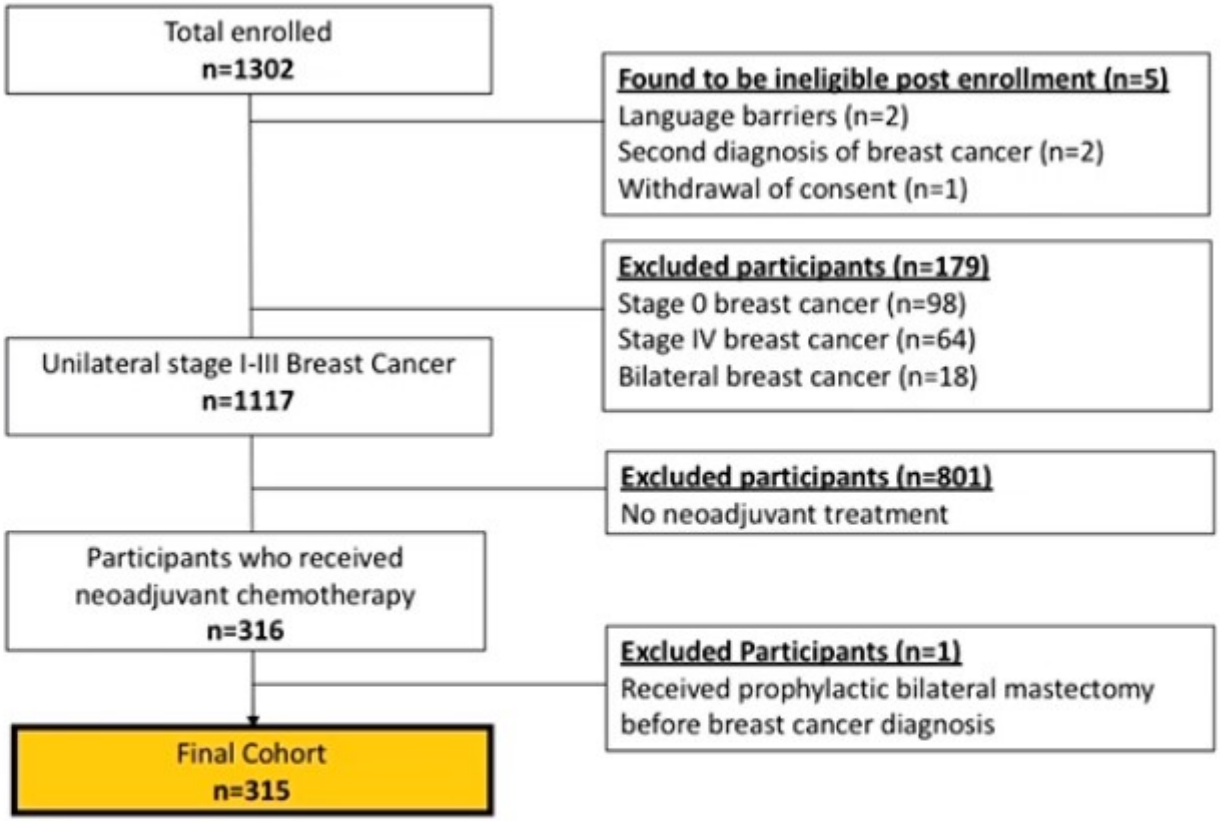
San Antonio Breast Cancer Symposium, December 4-8, 2018

Surgical treatment after neoadjuvant systemic therapy in young women with breast cancer: Results from a prospective cohort study

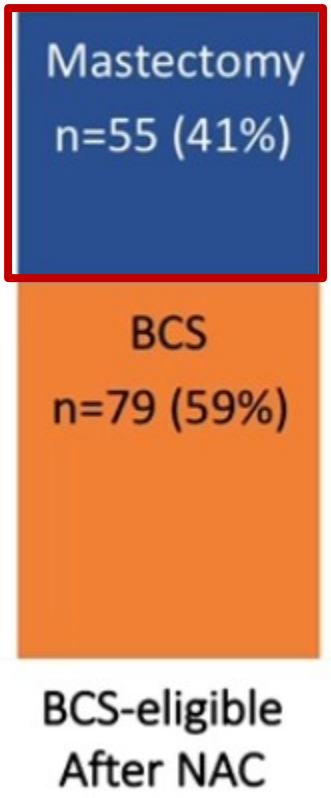
Hee Jeong Kim [1,2], Laura Dominici[1,3], Shoshana Rosenberg[1], Linda Ma Pak[1,3], Phillip D. Poorvu[1], Kathryn Ruddy[4], Rulla Tamimi[3], Lidia Schapira[5], Steven Come[6], Jeffrey Peppercorn[7], Virginia Borges[8], Ellen Warner[9], Hilde Vardeh[6], Laura Collins[6], Rachel Gaither[1], Tari King[1,3], Ann H. Partridge[1]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Asan Medical Center, Seoul, South Korea; [3]Brigham and Women's Hospital, Boston, MA; [4]Mayo Clinic, Rochester, MN; [5]Stanford University, Palo Alto, CA; [6]Beth Israel Deaconess Medical Center, Boston, MA;[7] Massachusetts General Hospital, Boston, MA; [8]University of Colorado Cancer Center, Aurora, CO; [9] Sunnybrook Health Science center, Toronto, ONT

Study Participants

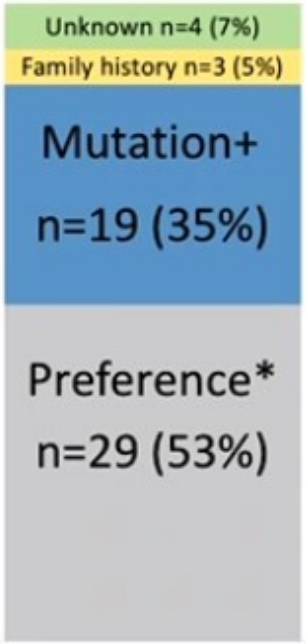


Initial surgical procedure among BCS-eligible patients after NAC (N=133)



- 41% of BCS-eligible patients after NAC chose mastectomy
- The proportion of patients with BCS as first surgical procedure was not influenced by response to NAC
  - 42% of BCS-eligible patients with clinical CR chose mastectomy
- Among BCS eligible patients who had mastectomy, 35% had a pCR

Reasons for choosing mastectomy in BCS-eligible patients (N=55)



- The most common documented reason that BCS-eligible patients chose mastectomy was patient preference (53%)
- 40% chose mastectomy because of carrying a BRCA 1 or 2, or p53 mutation or having a strong family history
- 75% who chose mastectomy underwent bilateral mastectomy
- Among BCS-eligible patients with cCR and/or ultimately pCR who chose mastectomy, these reasons were similar

*Preference was defined as someone who chose mastectomy without having a mutation or strong family history

What Drives Overtreatment?

- Many factors:
  - Defensive medicine
  - Financial interests
  - Challenge of generating evidence to support treatment de-escalation
  - Lag between evidence and clinical practice
  - Psychological factors

San Antonio Breast Cancer Symposium®, December 4 -8, 2018

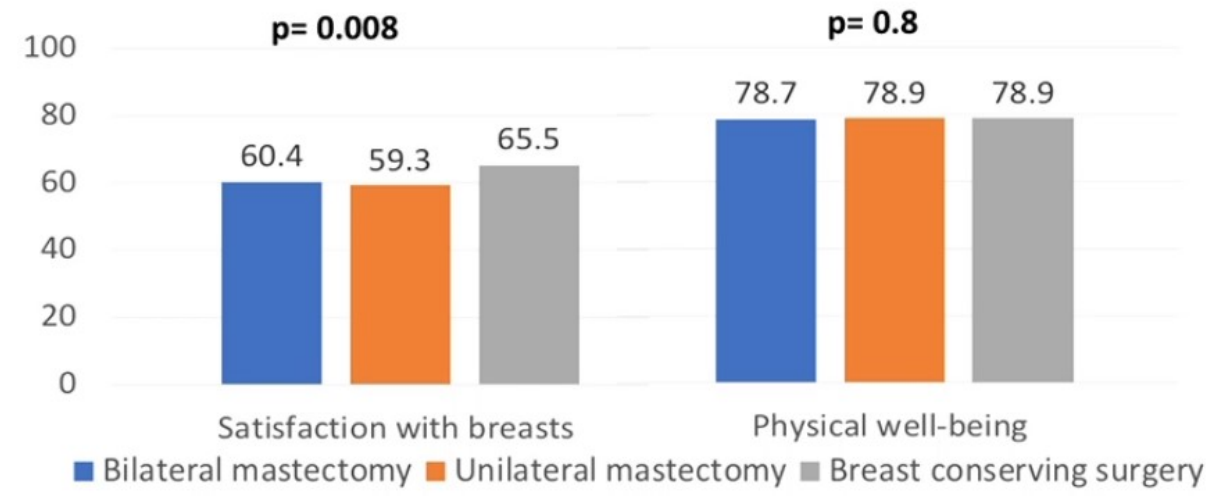
Local therapy and quality of life outcomes in young women with breast cancer

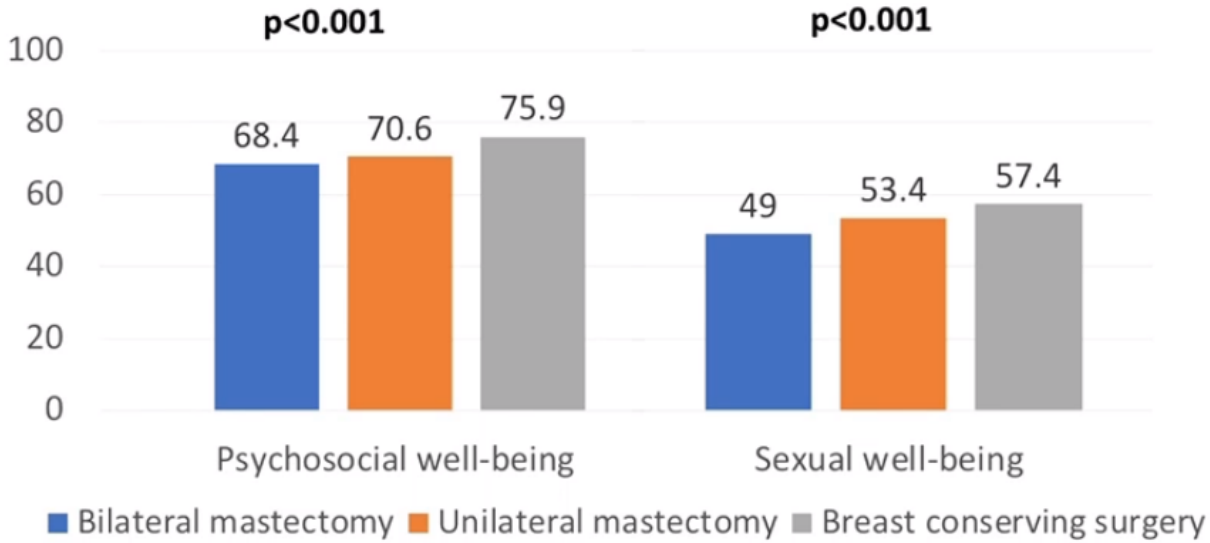
Laura Dominici, Jiani Hu, Tari King, Kathryn J. Ruddy, Rulla M. Tamimi, Jeffrey Peppercorn, Lidia Schapira, Virginia F. Borges, Steven E. Come, Ellen Warner, Ann Partridge, Shoshana Rosenberg

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

BREAST-Q Mean Scores

- Six domains:
  - Satisfaction with breasts
  - Psychosocial well-being
  - Physical well-being
  - Sexual well-being
  - Overall outcome
  - Process of care





Higher score = Better QOL

The Perils of Overtreatment: Worsened QoL

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prospective Study of Psychosocial Outcomes of Having Contralateral Prophylactic Mastectomy Among Women With Nonhereditary Breast Cancer

Patricia A. Parker, Susan K. Peterson, Yu Shen, Isabelle Bedrosian, Dalliah M. Black, Alastair M. Thompson, Jonathan C. Nelson, Sarah M. DeSnyder, Robert L. Cook, Kelly K. Hunt, Robert J. Volk, Scott B. Cantor, Wenli Dong, and Abenaa M. Brewster

- CPM associated with more body image distress ($p<0.001$) and poorer QOL ($p=0.02$)
- QOL similar before surgery but declined 1 month afterward and remained lower in CPM pts than in pts who did not have CPM

Considerazioni cliniche

- E’ opportuno considerare una mastectomia profilattica controlaterale (CPM) nelle pazienti BRCA MUT;
- Obiettivo dell’intervento: RIDUZIONE DEL RISCHIO DI NEOPLASIA MAMMARIA CONTROLATERALE;
- Consulenza genetica e Test BRCA più precocemente possibile;
- Cogliere il tempo della CHT neoadiuvante per indirizzare le pazienti a consulenza genetica, se indicato.