SAN ANTONIO BREAST CANCER SYMPOSIUM®

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

Young Breast Cancer patients: do they need a different surgery after NAC?

- Valentina Sini -

SISTEMA SANITARIO REGIONALE
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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

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Background

- Randomized controlled trials (RCTs) have demonstrated that eligibility for breast conserving surgery (BCS) can be increased after neoadjuvant chemotherapy (NAC)

- Despite eligibility for BCS, analyses from large pre-operative RCTs have revealed many women are undergoing mastectomy:
  - 76% of BCS eligible patients had mastectomy in CALGB 40601 (HER2+)
  - 69% of BCS eligible patients had mastectomy in CALGB 40603 (TNBC)

- Young women are more likely to present with large tumors and may benefit from a neoadjuvant systemic approach

- Recent data suggest that response rates, including pathologic complete response (pCR), are higher in women <40 years than in older women

- Little is known about how response to NAC influences surgical decision making in young women

Golshan et al 2015 Annals of Surg; Golshan et al 2016 BCRT

Loibl et al 2015 BCRT

Objectives

- To describe the use of and response to NAC among young women with breast cancer
- To evaluate choice of surgical procedure considering:
  - Before- and after- NAC eligibility for BCS
  - Clinical and pathological response to NAC
- To evaluate reasons for not undergoing BCS when BCS eligible after NAC

Methods

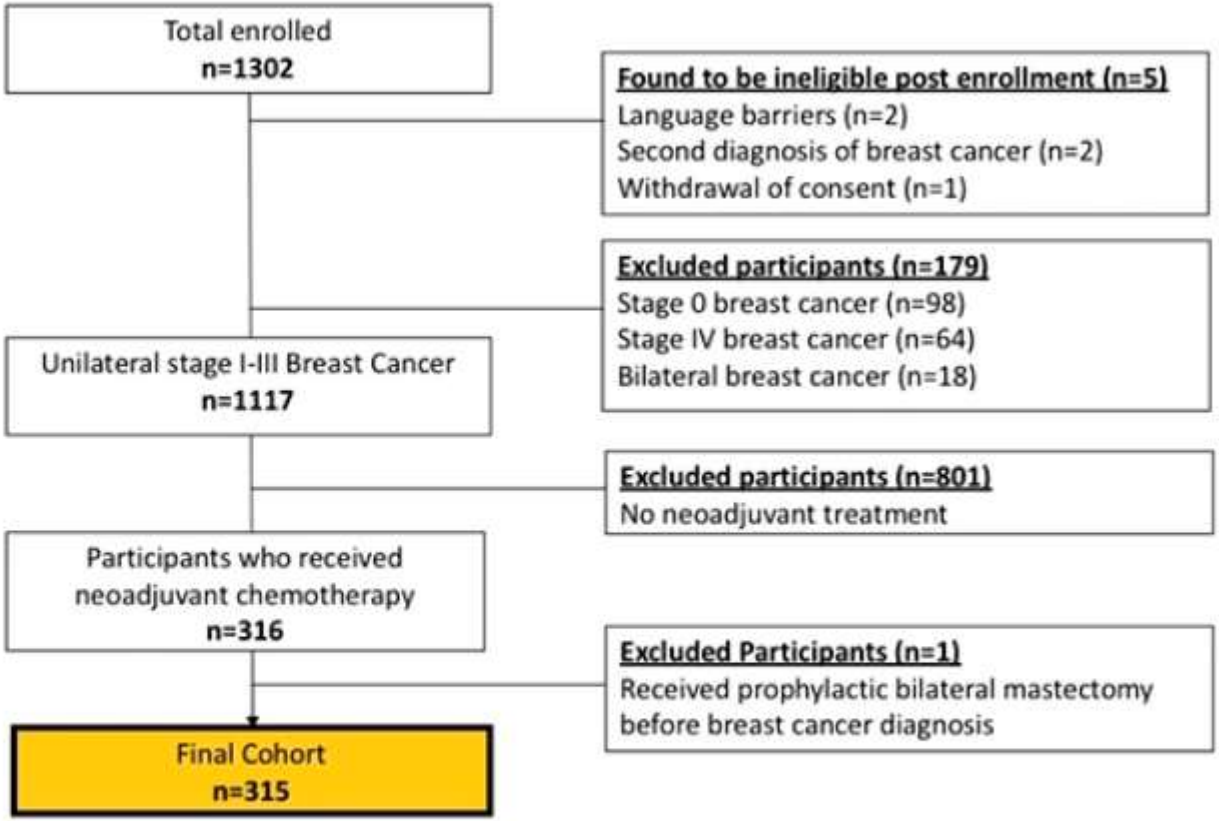
- The Young Women`s Breast Cancer Study (YWS)
  - Multicenter prospective cohort
  - Women age ≤40 at diagnosis of breast cancer identified through pathology record review
  - 12 participating hospitals (academic and community)
  - 1302 women enrolled from October 2006 to June 2016

- The study was established to explore biological, medical and psychosocial issues in young breast cancer patients

- Participants in YWS are enrolled after diagnosis and surveyed at baseline and in follow-up; medical records are reviewed serially

- For this analysis, patient characteristics were taken from baseline survey; medical records were reviewed to determine:
  - Tumor characteristics and stage
  - Eligibility for BCS (before and after NAC)
  - Clinical and pathologic response to NAC
  - BCS as initial procedure and definitive surgery
  - Reasons for mastectomy

Study Participants



Results: Patient Characteristics

	Characteristics	Number (N=315)	Percentage (%)
Age	Median (IQR)	36 yrs (32-38)	
Race/Ethnicity	Non Hispanic white	253	80
Clinical T stage	T1	36	11
	T2/T3	262	83
	T4	17	5
Clinical N stage	Node positive (N1-N3)	192	61
Clinical Subtypes	ER and or PR + / Her2 -	119	38
	Her2 positive	106	34
	Triple negative	90	29

Results: Clinical and Pathological Response

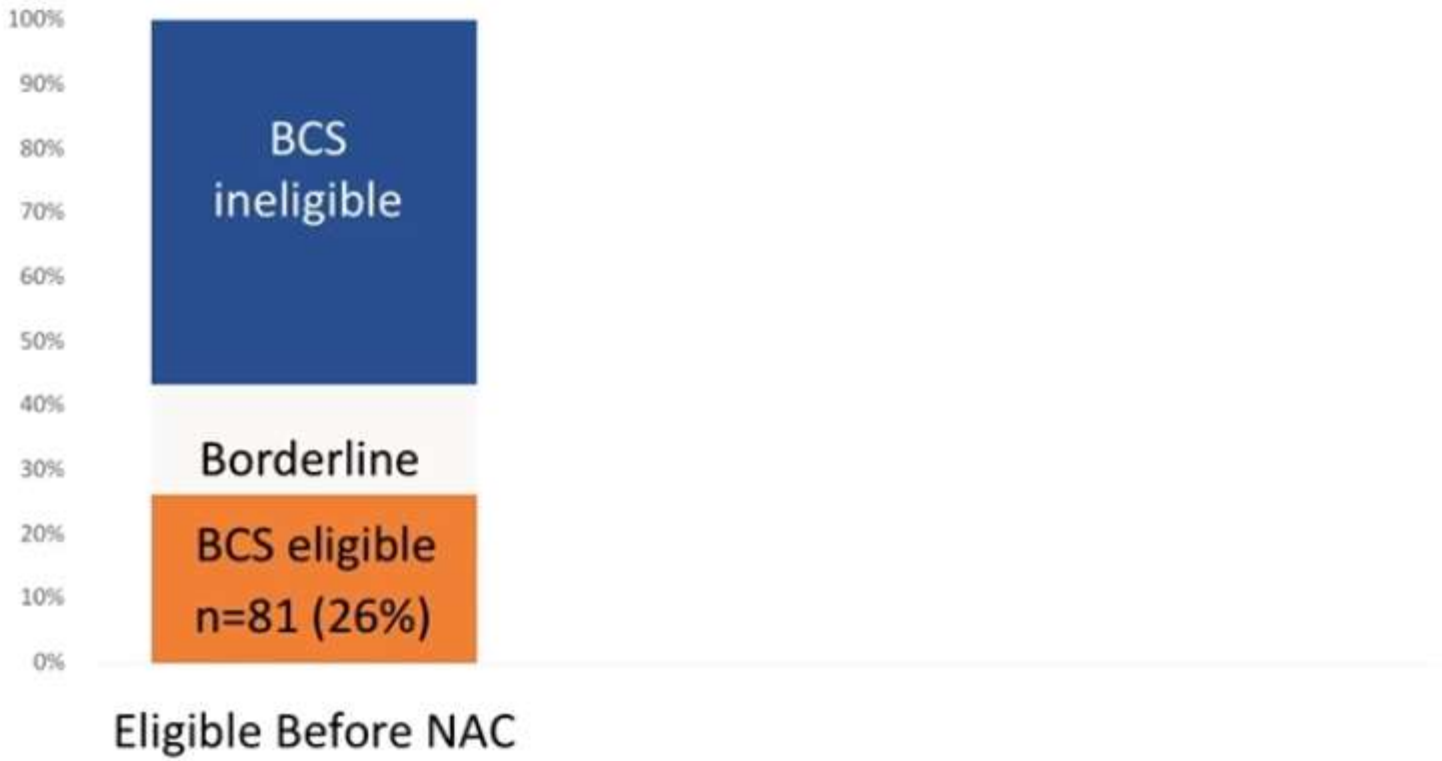
Response to NAC		Number (n=315)	Percentage (%)
Clinical Response	Complete Response(cCR)*	212	67
Pathologic Response	pCR (ypT0/isN0) †	100	32

Pathologic response by clinical subtype	pCR number	Percentage of pCR (%)
ER and or PR + / Her2 – *(n=119)*	21	18
Her2 positive *(n=106)*	42	40
Triple negative *(n=90)*	37	41

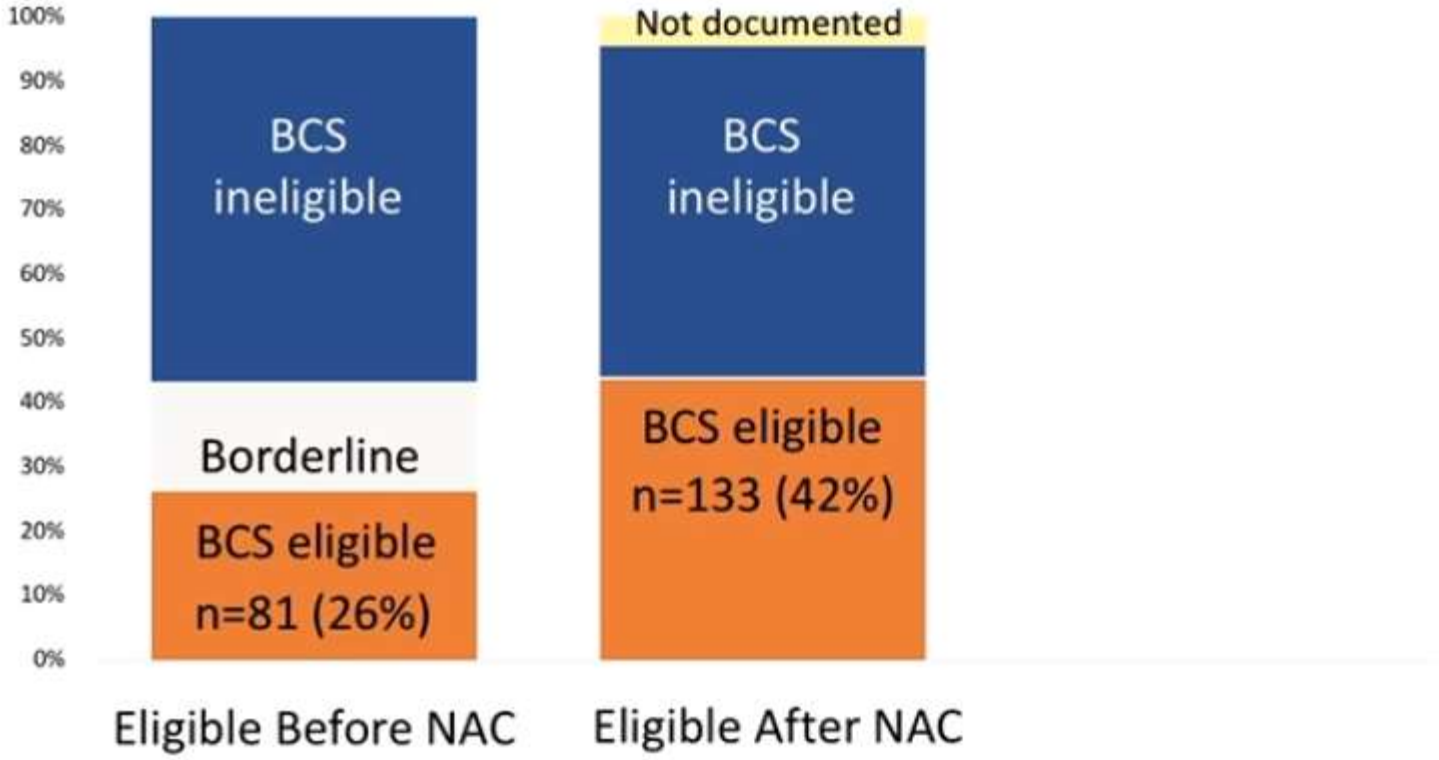
*cCR was defined as no palpable tumor in the breast

† pCR was defined as no tumor in the breast (with or without ductal carcinoma in situ) and absence of any tumor deposit more than 0.2mm in lymph nodes

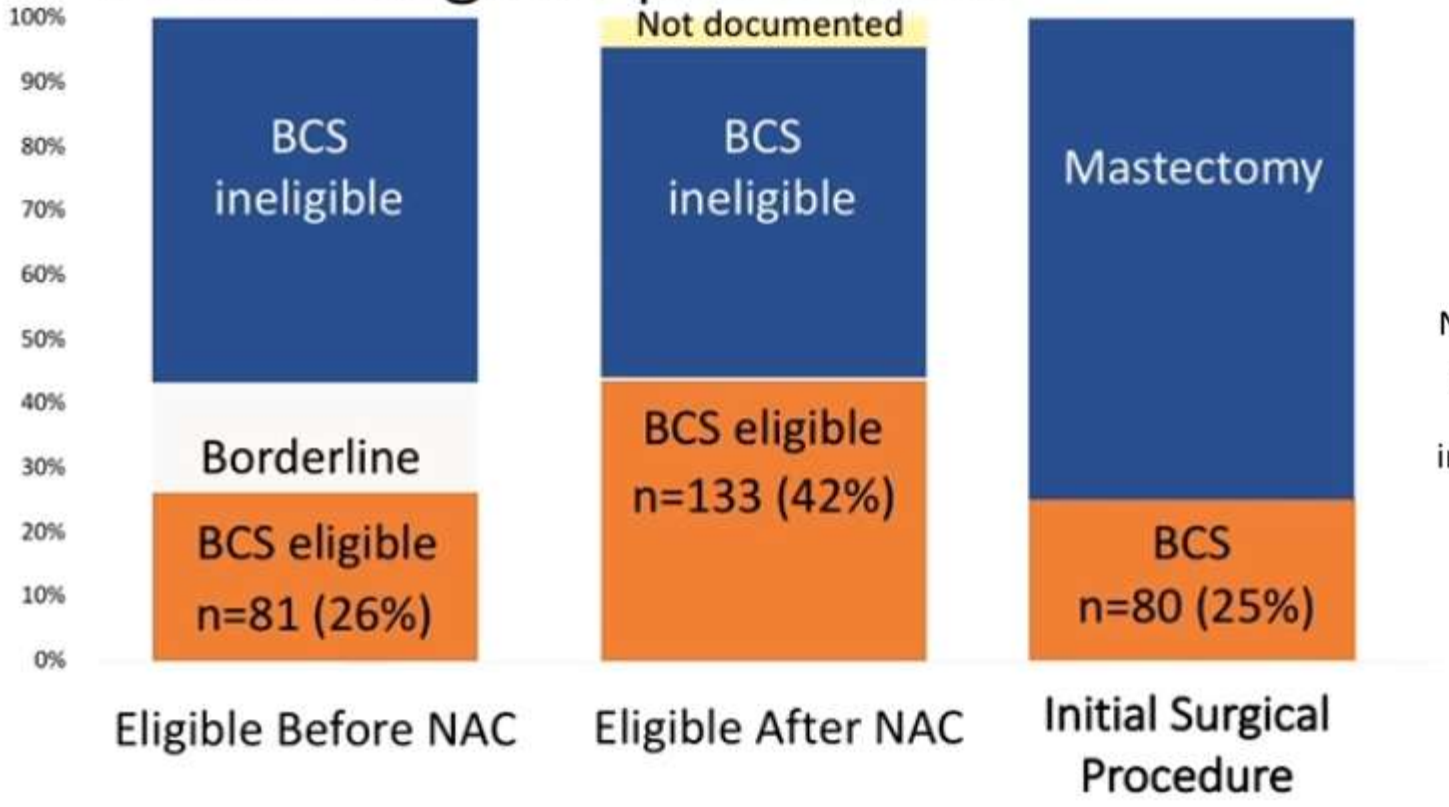
Change in BCS eligibility after NAC



Change in BCS eligibility after NAC

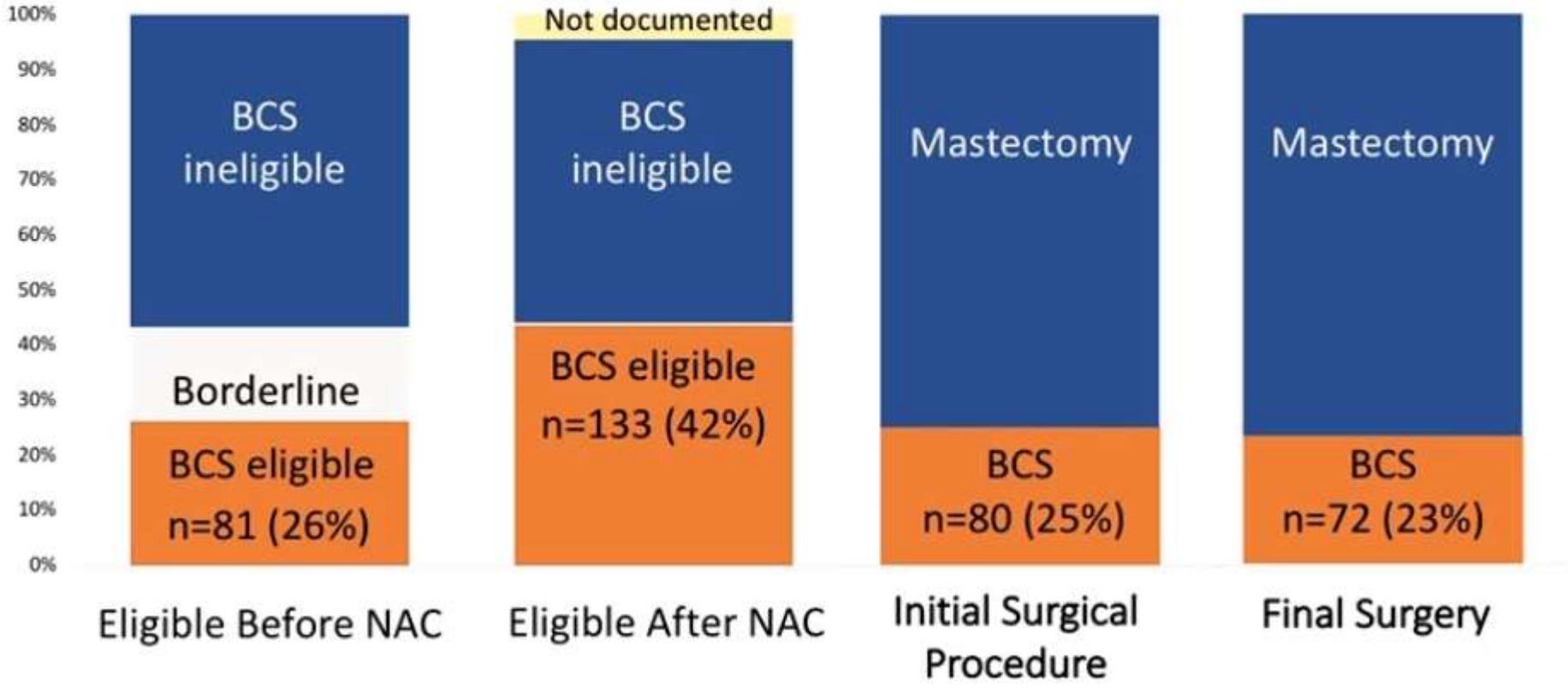


Change in BCS eligibility after NAC and initial surgical procedure

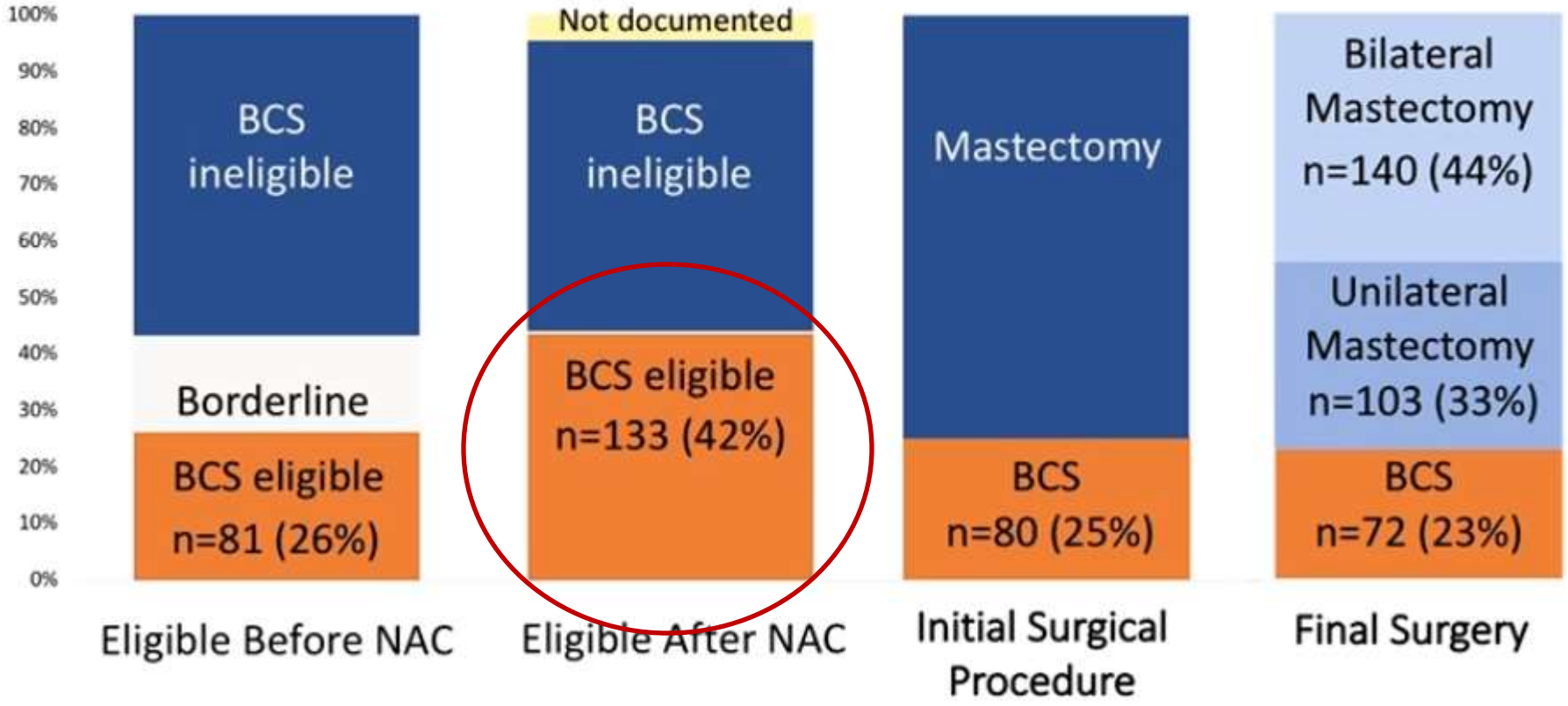


NAC **did not** change the proportion of patients with BCS as initial surgical procedure

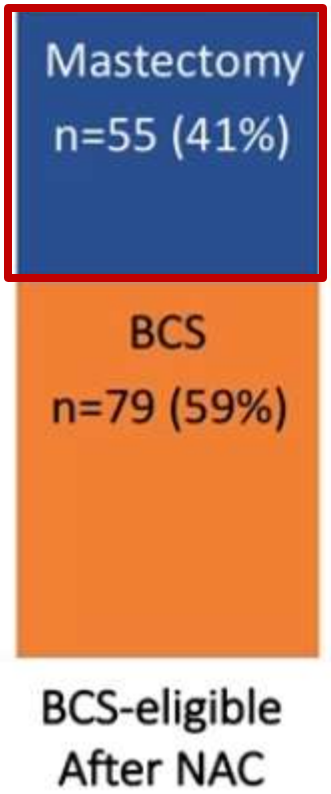
Change in BCS eligibility after NAC and surgery



Change in BCS eligibility after NAC and surgery

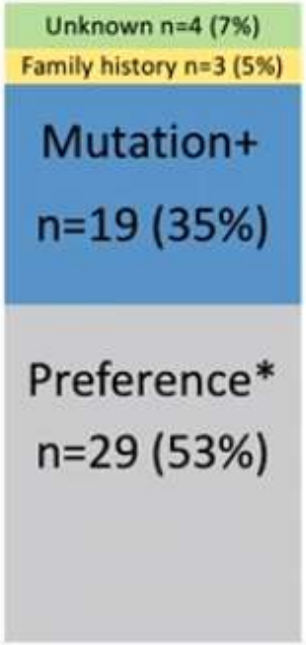


Initial surgical procedure among BCS-eligible patients after NAC (N=133)



- 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

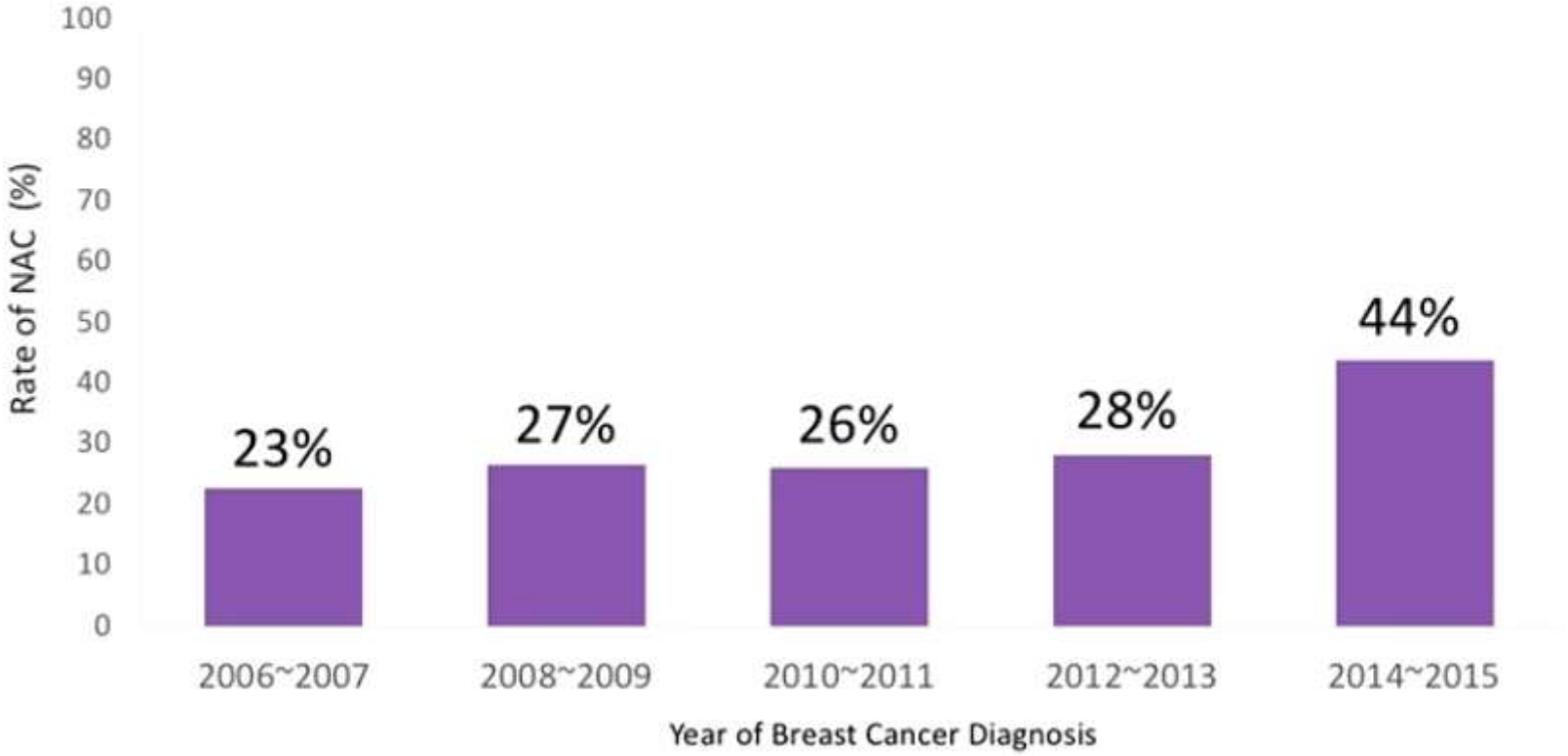
Reasons for choosing mastectomy in BCS-eligible patients (N=55)



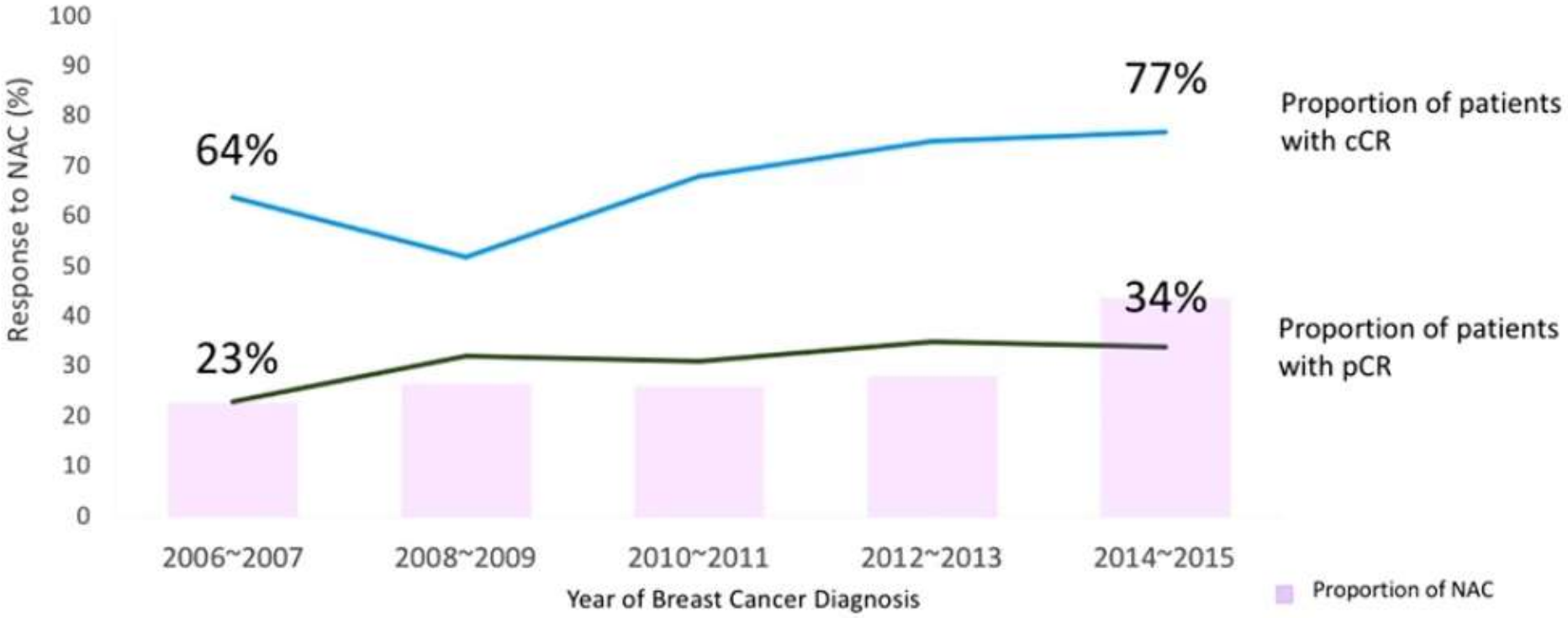
- The most common documented reason that BCS-eligible patients chose mastectomy was patient preference (53%)
- 40% chose mastectomy because of carrying a BRCA 1 or 2, or p53 mutation or having a strong family history
- 75% who chose mastectomy underwent bilateral mastectomy
- Among BCS-eligible patients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

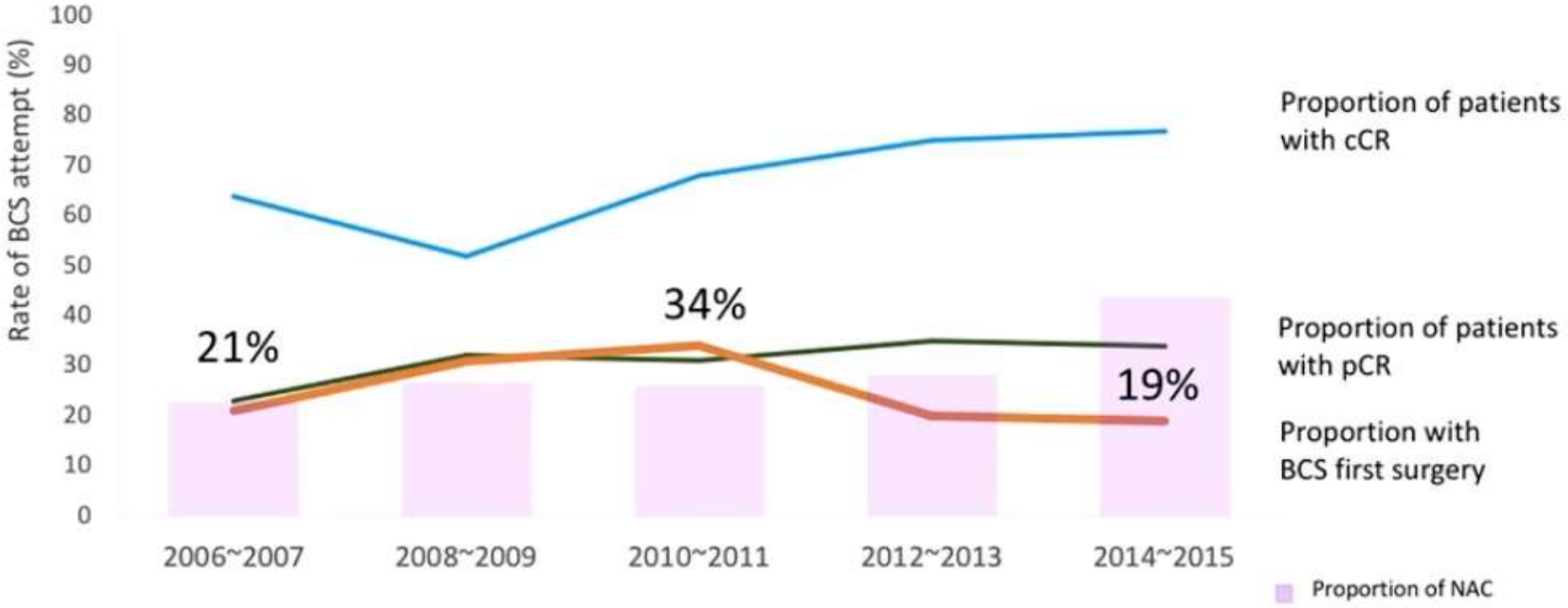
Exploratory analysis: NAC use over time in YWS



Exploratory analysis: NAC use and response over time in YWS



Exploratory analysis: NAC use and response, and BCS as first surgery over time



Conclusions and Implications

- NAC increased the proportion of young women with breast cancer who were eligible for BCS, yet 40% of eligible patients chose mastectomy regardless of response to NAC in a large multicenter cohort
  - Personal preference (without known high risk predisposition) was most common reason
- While rates of NAC have increased over time and response rates have improved, rate of BCS as first surgical procedure is not increasing
- Surgical decisions among young women with breast cancer appear driven by factors beyond the extent of disease and response to NAC
- Focused efforts to optimize surgical decision-making are needed

What Drives Overtreatment?

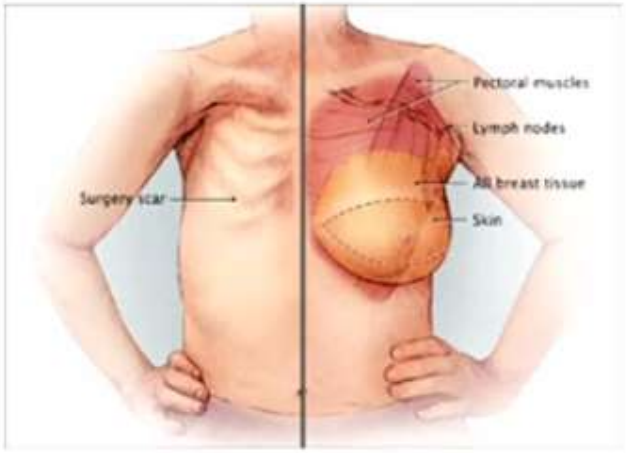
- Many factors:
  - Defensive medicine
  - Financial interests
  - Challenge of generating evidence to support treatment de-escalation
  - Lag between evidence and clinical practice
  - Psychological factors

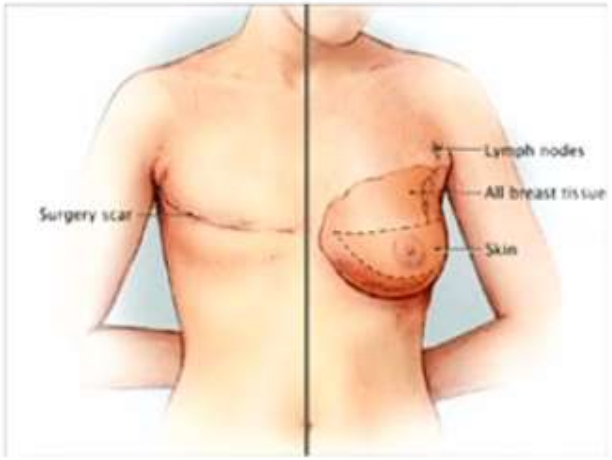
De-escalation

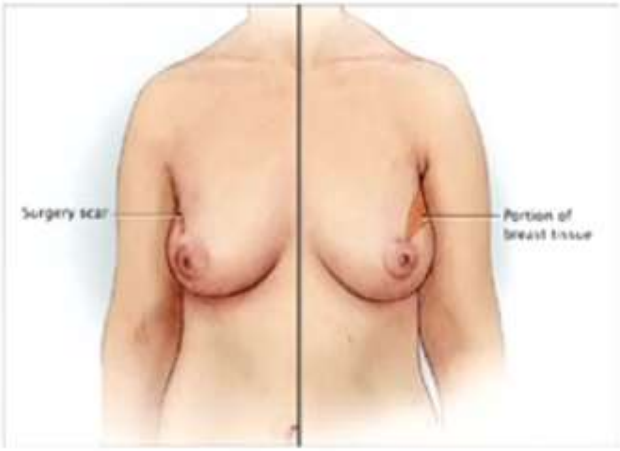
- Perhaps more than for any other type of cancer, the management of breast cancer has been supported by a steady trajectory of research that has discovered ways to:
  - safely de-escalate therapy and
  - identify patients who may safely forego potentially toxic treatments

Surgery

- From Radical Mastectomy to MRM to BCT







RCTs of MRM vs BCT: Milan 1973; NSABP B-06 1976; EORTC 1980; DBCG 82TM 1983; NCI 1979; IGR 1972

Radiotherapy

- From longer to shorter courses:
  - Hypofractionated whole breast irradiation
    - Long-term data from large RCTs (e.g., START A & B, Canadian trials)
  - Accelerated partial breast irradiation
    - Large RCTs completed and presented in this very meeting

Systemic therapy

- HER2+ disease
  - 3-yr IDFS 98.7% in 406 pts with node-negative tumors ≤3 cm treated with weekly paclitaxel and trastuzumab x 12 + 9 mos trastuzumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

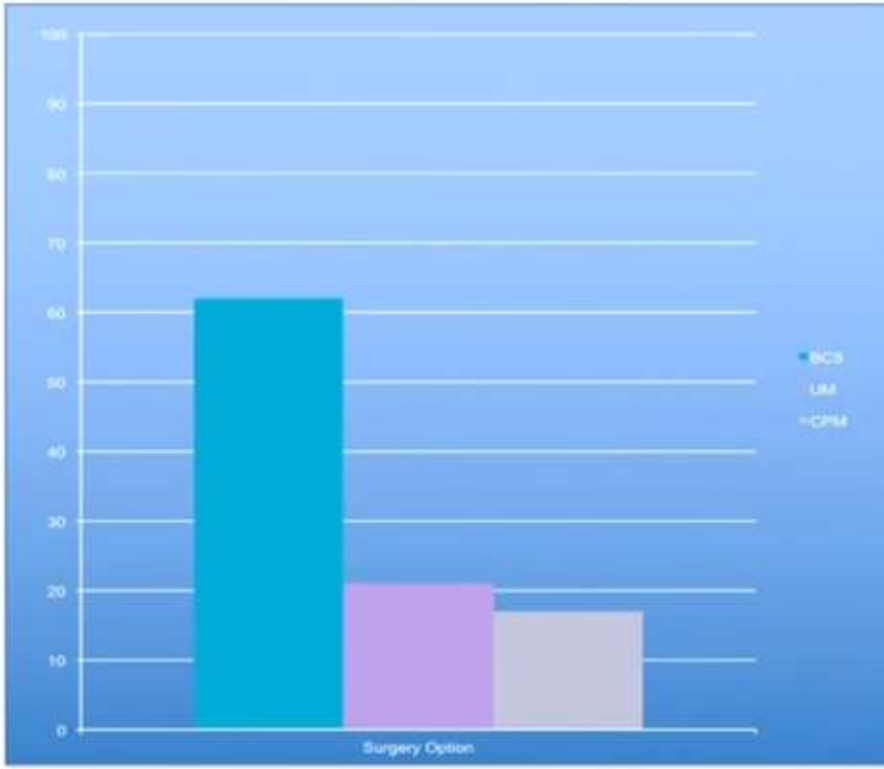
Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

CPM Receipt

Jagsi et al. JAMA Surgery 2017.

The JAMA Network

- Pts w unilateral early-stage breast cancer identified by 2 SEER registries in 2013-14
- 62% received BCS, 21% unilateral mastectomy, and 17% bilateral mastectomy with CPM
- Even among women without deleterious genetic mutation or FH in multiple relatives, 14% received CPM



CanSORT
www.cansort.org

CPM: contralateral prophylactic mastectomy

The Challenge

- Despite robust evidence showing that many women can safely be spared potentially toxic treatments…
  - Many women diagnosed with breast cancer today pursue considerably more aggressive treatments than needed to achieve excellent outcomes in terms of survival and recurrence

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

Background

- More than 13,000 women ≤40 years of age are diagnosed with breast cancer each year
  - ~7% of new breast cancers diagnosed in the United States

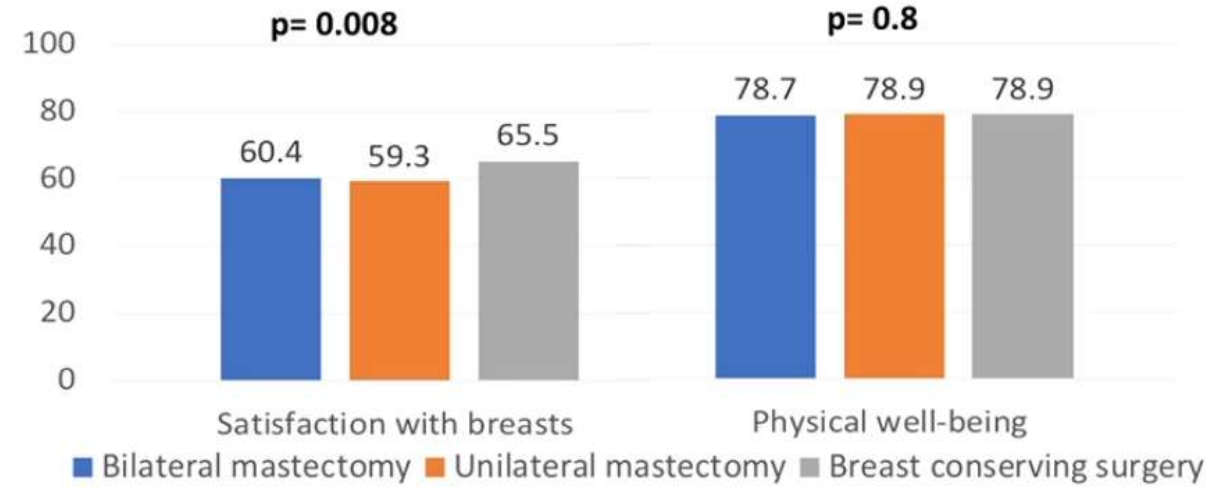
- Despite equivalent local regional control and survival with breast conservation and mastectomy, rates of (bilateral) mastectomy are increasing in young women
  - 3.6% in 1998 → 33% in 2011

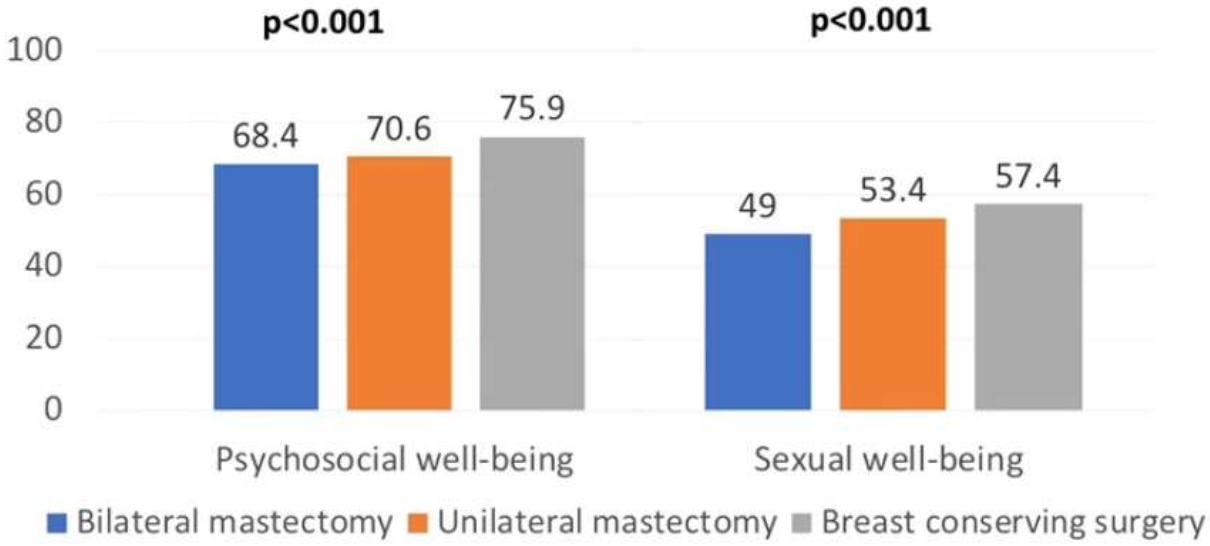
- Little is known about the impact of surgery, particularly in the era of increasing bilateral mastectomy, on QOL in young survivors

Anders Semin Oncol 2009
Kurian JAMA 2014
Aalders JCO 2016

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

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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

Conclusions

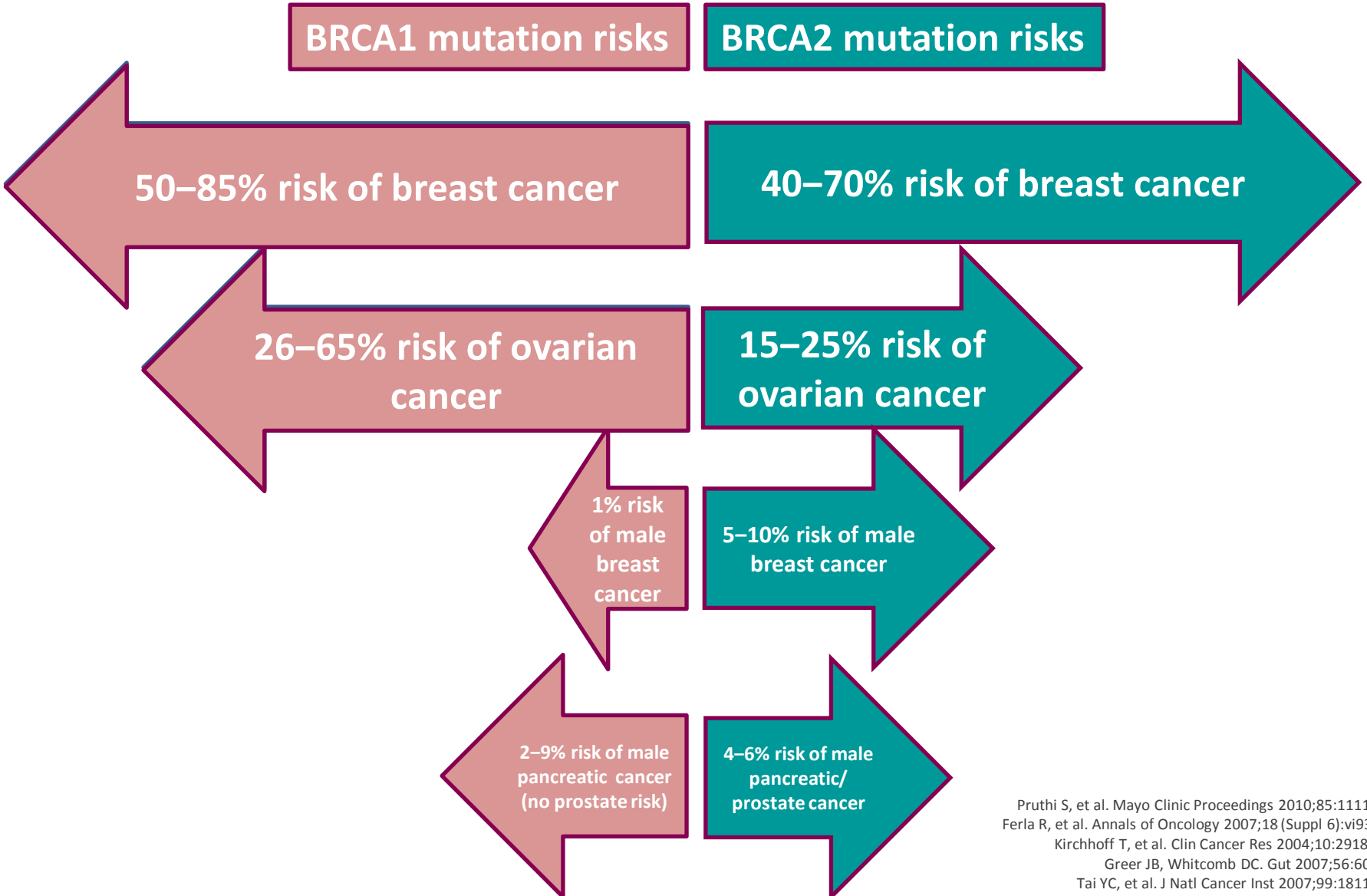
- Local therapy decisions are associated with a persistent impact on QOL in young breast cancer survivors
- Compared to BCS, unilateral or bilateral mastectomy is associated with significant decreases in QOL domains for:
  - Satisfaction with breasts
  - Psychosocial well-being
  - Sexual well-being
- Knowledge of the potential long term impact of surgery on QOL is of critical importance for counseling young women about surgical decisions

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

BRCA ESSENTIALS

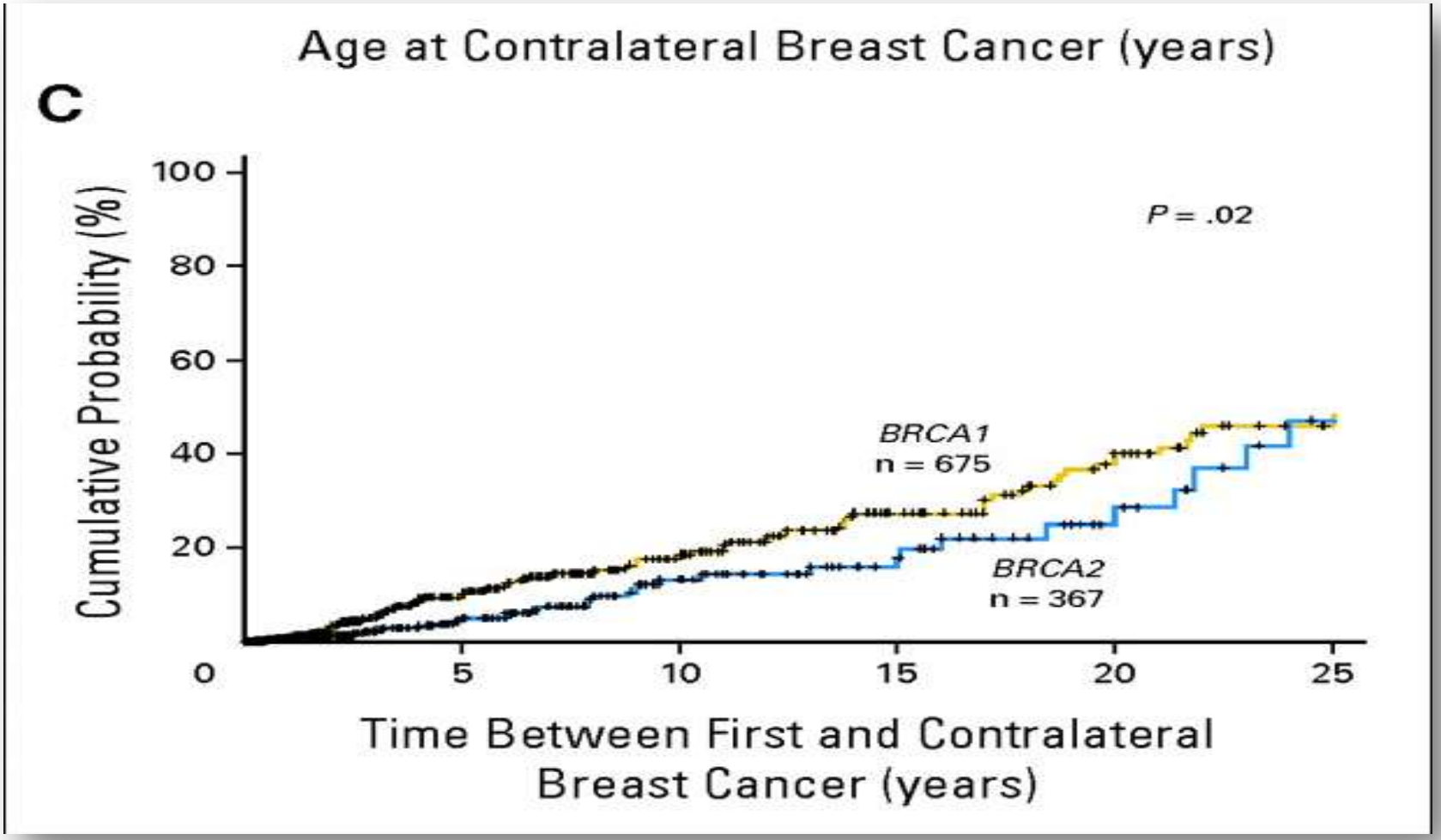
- Approximately **5%** of unselected patients with BC carry a germline mutation in **BRCA1 and BRCA2**.
- BRCA1 and BRCA2 are tumour-suppressor genes located on chromosomes **17q21** and **13q12**, respectively
- BRCA1 and BRCA2 are key components of the **homologous recombination pathway**, and cells that lack these proteins are unable to repair double strand brakes by homologous recombination.
- Tumourigenesis in germline BRCA1/2 pathogenic mutation carriers generally follows a two-hit hypothesis, by somatic inactivation of the second-wild-type allele.
- Patients with a **BRCA1** mutation are predisposed to **TNBC**, whereas patients with a **BRCA2** mutation most often have tumors that express **estrogen receptors**.

RISKS OF DEVELOPING SPECIFIC CANCERS VARIES BETWEEN CARRIERS OF BRCA1 AND BRCA2 MUTATIONS



Pruthi S, et al. Mayo Clinic Proceedings 2010;85:1111–1120.
Ferla R, et al. Annals of Oncology 2007;18 (Suppl 6):vi93–vi98.
Kirchhoff T, et al. Clin Cancer Res 2004;10:2918–2921.
Greer JB, Whitcomb DC. Gut 2007;56:601–605.
Tai YC, et al. J Natl Cancer Inst 2007;99:1811–1814.

CUMULATIVE RISK OF CONTRALATERAL BREAST CANCER AFTER FIRST BC IN BRCA1/2 POSITIVE



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

GENETIC EVALUATION AND TESTING

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).*

RISK-REDUCING SURGERY

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

Xiao Li et al, Clin Cancer Res 2016; Rebbeck et al. J Natl Canc Inst 2009; Finch et al. J Cl Oncol 2014

MY CONCLUSIONS

- The young age in itself is not an indication to a different surgery
- Local therapy decisions are associated with a persistent impact on QoL in young breast cancer survivors
- Avoid overtreatment
- *Take advantage of the time of neoadjuvant CT to address young patients to genetic counseling if indicated*
- Recommend bilateral mastectomy (with CPM) to BRCA 1-2 carriers

THANKS