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BRCA mutation Carriers with early breast cancer Debate: Breast Conservation Surgery (BCS) vs. Mastectomy

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Genetics in Clinical Cancer Care: From Family Reunions to the Frontline of Developmental Therapeutics
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The University of Chicago

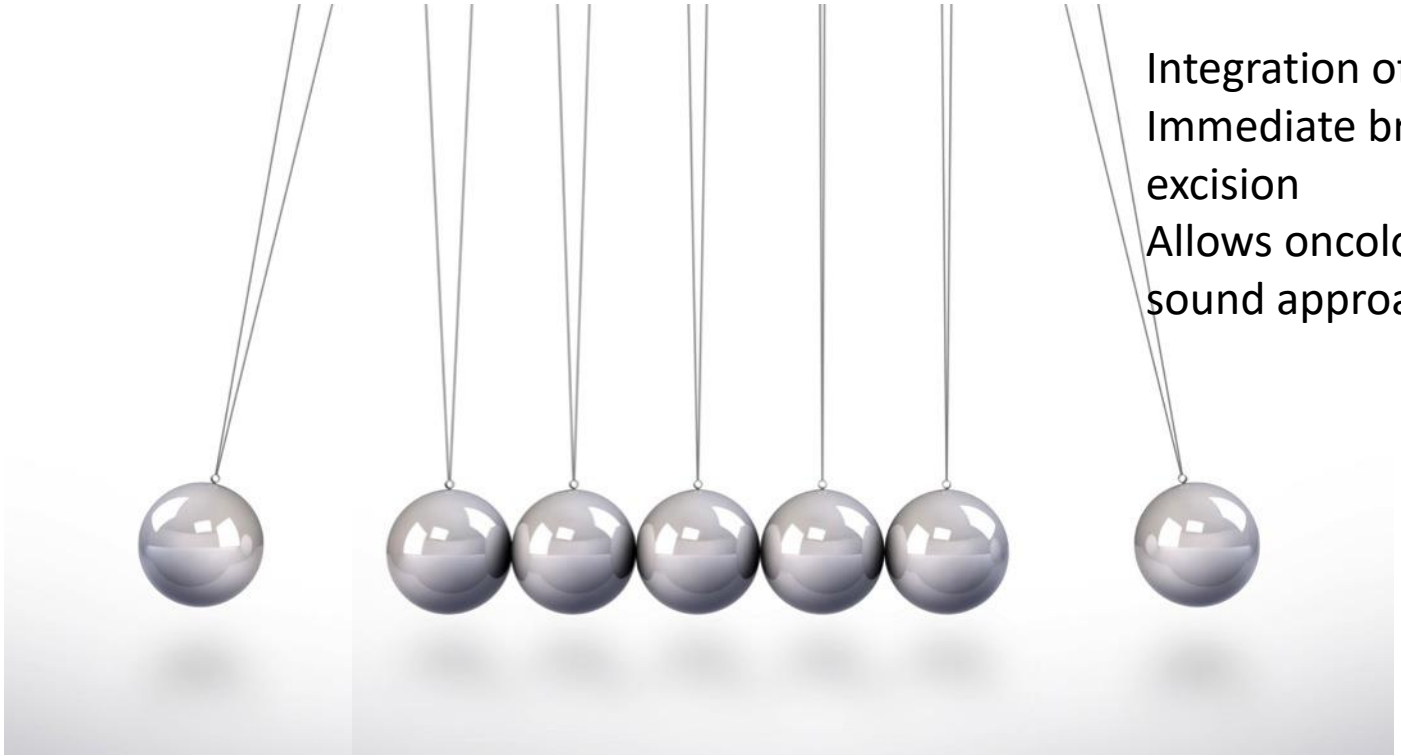
Hong Kong Hereditary Breast Cancer Family Registry
香港遺傳性乳癌家族資料庫

Breast Ovarian Prostate Hereditary Cancers

Disclosures-

- Astrazenaca supported research programme

Mastectomy → Lumpectomy → Oncoplastic surgery



Integration of plastic surgery techniques
Immediate breast reshaping after wide excision
Allows oncologically and cosmetically sound approach

Breast Conservation Surgery

SAME
Overall Survival

Mastectomy

Better body image
Better psychological outcome

Ann Surg Oncol (2014) 21:704–716
DOI 10.1245/s10434-014-3481-4

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

ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD[1], Stuart J. Schnitt, MD[2], Armando E. Giuliano, MD[3], Jay R. Harris, MD[4], Seema A. Khan, MD[5], Janet Horton, MD[6], Suzanne Klimberg, MD[7], Mariana Chavez-MacGregor, MD[8], Gary Freedman, MD[9], Nehmat Houssami, MD, PhD[10], Peggy L. Johnson[11], and Monica Morrow, MD[12]

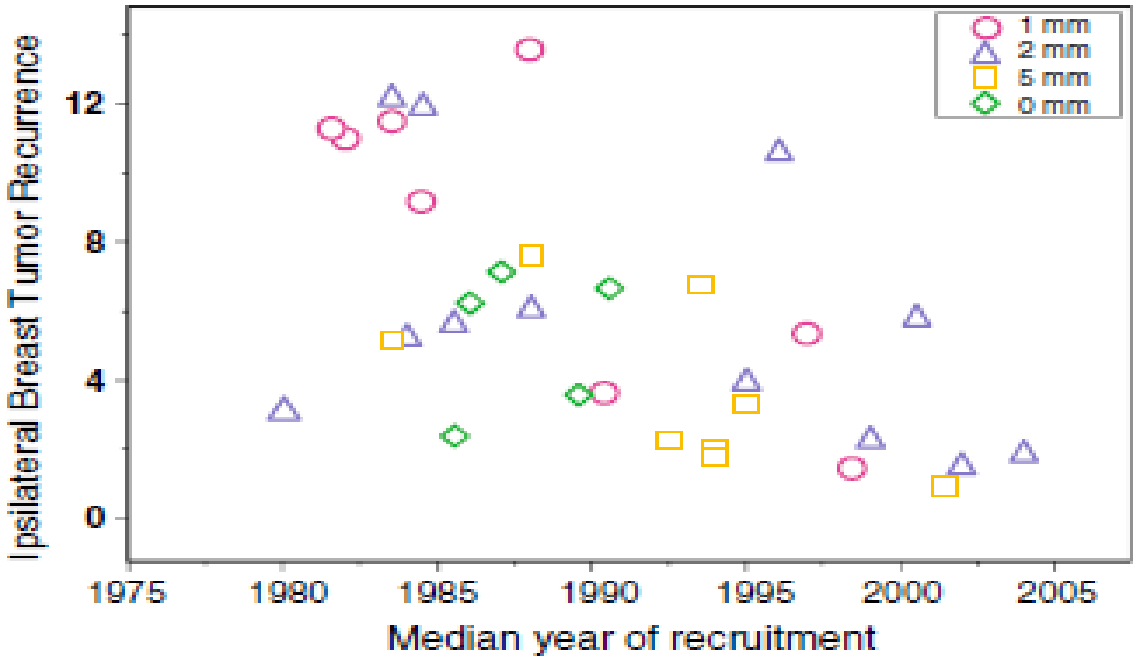


FIG. 1 Scatter plot of unadjusted rates of ipsilateral breast tumor recurrence by median year of study recruitment

Clinical question	Recommendation	Level of evidence
What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?	Positive margins, defined as ink on invasive cancer or DCIS, are associated with at least a two-fold increase in IBTR. This increased risk in IBTR is not nullified by: delivery of a boost, delivery of systemic therapy (endocrine therapy, chemotherapy, biologic therapy), or favorable biology	Meta-analysis and secondary data from prospective trials and retrospective studies
Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?	Negative margins (no ink on tumor) optimize IBTR. Wider margins widths do not significantly lower this risk. The routine practice to obtain wider negative margin widths than ink on tumor is not	Meta-analysis and retrospective studies
require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin?	LCIS at the margin is not an indication for re-excision. The significance of pleomorphic LCIS at the margin is uncertain	
Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (<40 years)?	Young age (≤40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features. There is no evidence that increased margin width nullifies the increased risk of IBTR in young patients	Secondary data from prospective randomized trials and retrospective studies
What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?	An EIC identifies patients who may have a large residual DCIS burden after lumpectomy. There is no evidence of an association between increased risk of IBTR when margins are negative	Retrospective studies

Conclusion. The use of no ink on tumor as the standard for an adequate margin in invasive cancer in the era of multi-disciplinary therapy is associated with low rates of IBTR and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.

IBTR ipsilateral breast tumor recurrence, *DCIS* ductal carcinoma in situ, *WBRT* whole breast radiation therapy, *LCIS* lobular carcinoma in situ, *BCT* breast-conserving therapy, *EIC* extensive intraductal component

What about in BRCA mutation carriers

Breast Conservation Surgery vs Mastectomy

A Systematic Review

Co M , Kwong A et al . Clinical Breast Cancer 2019

Local recurrence

Years after surgery	Range (%)		Median (%)		Pooled (%)	
	BCS	M	BCS	M	BCS	M
5	2 - 22	1.4 - 9	13.3	5.2	8.2	3.4
10	10.5 - 52	5.5 - 9	16.2	7.3	15.5	4.9
15	15.8 - 49	5.5 - 9.4	23.8	7.3	23.0	6.4

BCS = Breast conserving surgery; M = Mastectomy

Conclusion: More local recurrence at 5, 10 and 15 years after BCS compared to mastectomy

Co M , Kwong A et al . Clinical Breast Cancer 2019

Survival (Breast cancer specific survival)

Study	Design	Patient characteristics	Breast cancer specific survival / patients undergone surgery (%)					
			5-year		10-year		15-year	
			BCS	Mastectomy	BCS	Mastectomy	BCS	Mastectomy
Robson et al, 2005	Case series	T1 - T2	84/87 (96.9)	-	78/87 (90.1)	-	-	-
Garcia-etienne et al, 2009	Retrospective cohort	pT1 - T3	-	-	283/302 (93.6)	330/353 (93.5)	-	-
Overall	-	-	**84/87 (96.9)**	-	**361/389 (92.8)**	**330/353 (93.5)**	-	-

Co M , Kwong A et al . Clinical Breast Cancer 2019

Survival (Distant disease free survival)

Study	Design	Patient characteristics	Distant disease free survival / patients undergone BCS (%)		
			5-year	10-year	15-year
Robson et al, 2005	Cohort	T1 - 2	81/87 **(92.9)**	76/87 **(87.3)**	-

Co M , Kwong A et al . Clinical Breast Cancer 2019

Survival (Overall survival)

Study	Design	Patient characteristics	Overall survival / patients undergone surgery (%)					
			5-year		10-year		15-year	
			BCS	M	BCS	M	BCS	M
Robson et al, 2005	Case series	T1 - 2	85/87 (95.6)	-	78/87 (89.4)	-	-	-
Garcia-etienne et al, 2009	Retrospective cohort	pT1 - T3	-	-	278/302 (92.1)	324/353 (91.8)	264/302 (87.3)	317/353 (89.8)
Martin et al, 2014	Prospective cohort	Stage I - III	36/45 (80)	97/117 (83)	31/45 (68)	80/117 (68)	26/45 (58)	74/117 (63)
Pierce et al, 2000	Retrospective cohort	-	61/71 (86)	-	-	-	-	-
Overall	-	-	**182/203 (89.7)**	**97/117 (83)**	**387/434 (89.0)**	**404/470 (86.0)**	**290/347 (83.6)**	**391/470 (83.2)**

Co M , Kwong A et al . Clinical Breast Cancer 2019)

Ipsilateral Breast Cancer Recurrence

Risk factors	No. of studies (patients)	IBR hazard ratio (95% CI)	Heterogeneity		Studies by quality			Consistency	Level of evidence
			I^2 (%)	P value	High	Moderate	Low		
Age (continuous)	1 (160)	0.96 (0.92-0.99)	-	-	0	1	0	-	Inconclusive
Age >50 years old	1 (396)	0.69 (0.27-1.77)	-	-	1	0	0	-	Inconclusive
Positive margins	1 (160)	0.76 (0.18-3.19)	-	-	1	0	0	-	Inconclusive
Positive ER-status	1 (396)	1.74 (0.71-4.25)	-	-	1	0	0	-	Inconclusive
Grade III	1 (396)	0.95 (0.35-2.59)	-	-	1	0	0	-	Inconclusive
T status (≥ T2)	1 (396)	0.76 (0.37-1.53)	-	-	1	0	0	-	Inconclusive
Stage II	1 (160)	0.69 (0.36-1.89)	-	-	1	0	0	-	Inconclusive
Positive nodal status	1 (396)	0.86 (0.39-1.89)	-	-	1	0	0	-	Inconclusive
Tamoxifen use	2 (556)	0.73 (0.39-1.39)	0	0.58	1	1	0	Consistent	Moderate
Tamoxifen use (patients who did not undergo bilateral oophorectomy)	1 (160)	0.39 (0.09-1.69)	-	0	0	1	0	-	Inconclusive
Chemotherapy	2 (556)	0.51 (0.31-0.84)	0	0.86	1	1	0	Consistent	Moderate
Oophorectomy	2 (556)	0.42 (0.22-0.81)	0	0.43	1	1	0	Consistent	Moderate

IBR ipsilateral breast cancer, CI confidence interval, ER estrogen-receptors

Valachis et al. 2014. Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014; 144(3): 443–455

Systematic Review on BCS vs Mastectomy in BRCA mutation carriers

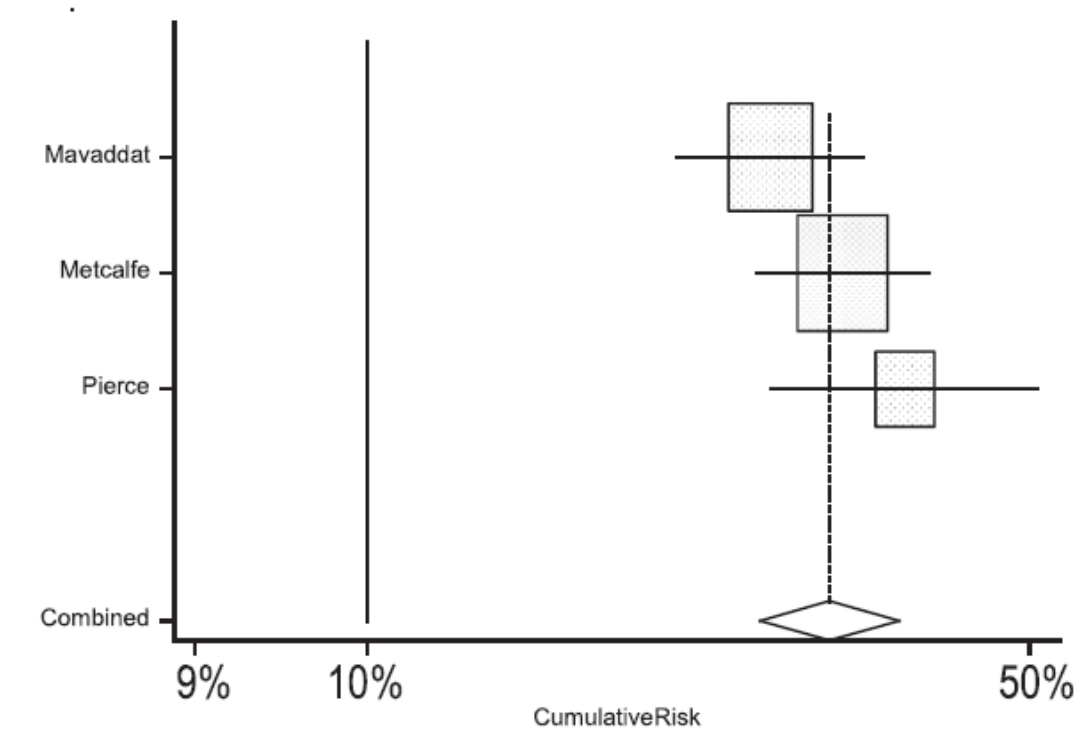
- Survival between BCS and mastectomy is comparable in BRCA patients
  - Even-though local recurrence rate is higher in BCS group
- LR is related to use of chemotherapy , tamoxifen, salpingo-oopherectomy
- Theoretical cosmetic advantage in BCS group

BCS should be offered

Co M , Kwong A et al . Clinical Breast Cancer 2019

Patients with *BRCA* mutation have high rate of contralateral breast cancers (CBC)

- 5 year risk of CBC is *BRCA*1 15% and *BRCA2* 9%
- CBC risk increases with length of time following first diagnosis
- If she develops right breast cancer then likely she will need additional chemo



C3

Cumulative risk = 33%; 95% CI: 27%-39%
Test for heterogeneity: Q = 4.071 (p=0.131)

Molina-Montes et al. The Breast 23:721, 2014.

An increasing trend of prophylactic mastectomy in the West

Table 1 Studies examining trends in CPM in the US

Study	Year published	Study period	Percentage increase in CPM of all patients over the study period	Percentage increase in CPM of all mastectomy patients over the study period	Data source
Tuttle et al[14] (invasive cancer)	2007	1998–2003	2.7	6.8	SEER
Tuttle et al[15] (DCIS)	2009	1998–2005	3.1	12.0	SEER
Jones et al[17]	2009	1998–2007	NA	9.6	Ohio state-NCCN network
Yao et al[16]	2010	1998–2007	4.3	NA	NCDB
King et al[11]	2011	1997–2005	NA	17.5	MSKCC single institution
Pesce et al[20]	2014	2003–2010	5.6	NA	NCDB
Kurian et al[19]	2014	1998–2011	10.3	NA	California Cancer Registry
Kummerow et al[18]	2015	1998–2011	9.3	24.3	

Abbreviations: CPM, contralateral prophylactic mastectomy; SEER, Surveillance Epidemiology End Results; DCIS, ductal carcinoma in situ; NA, not available; NCDB, National Cancer Data Base; NCCN, National Comprehensive Cancer Network; MSKCC, Memorial Sloan Kettering Cancer Center.

Yao et al. International Journal of Women's Health 2016:8

The “Angelina Jolie” EFFECT- What happened

- 14 May 2013 the BRCA1 mutation carrier status
- A non-affected carrier
- Family history of breast and ovarian cancer
- Announcement of a personal risk of 87% of breast cancer and 50% of ovarian cancer
- Announcement of decision to undergo risk reduction mastectomy to reduce to 5%
- Announcement of decision to undergo risk reduction bilateral salpingo-oophorectomy

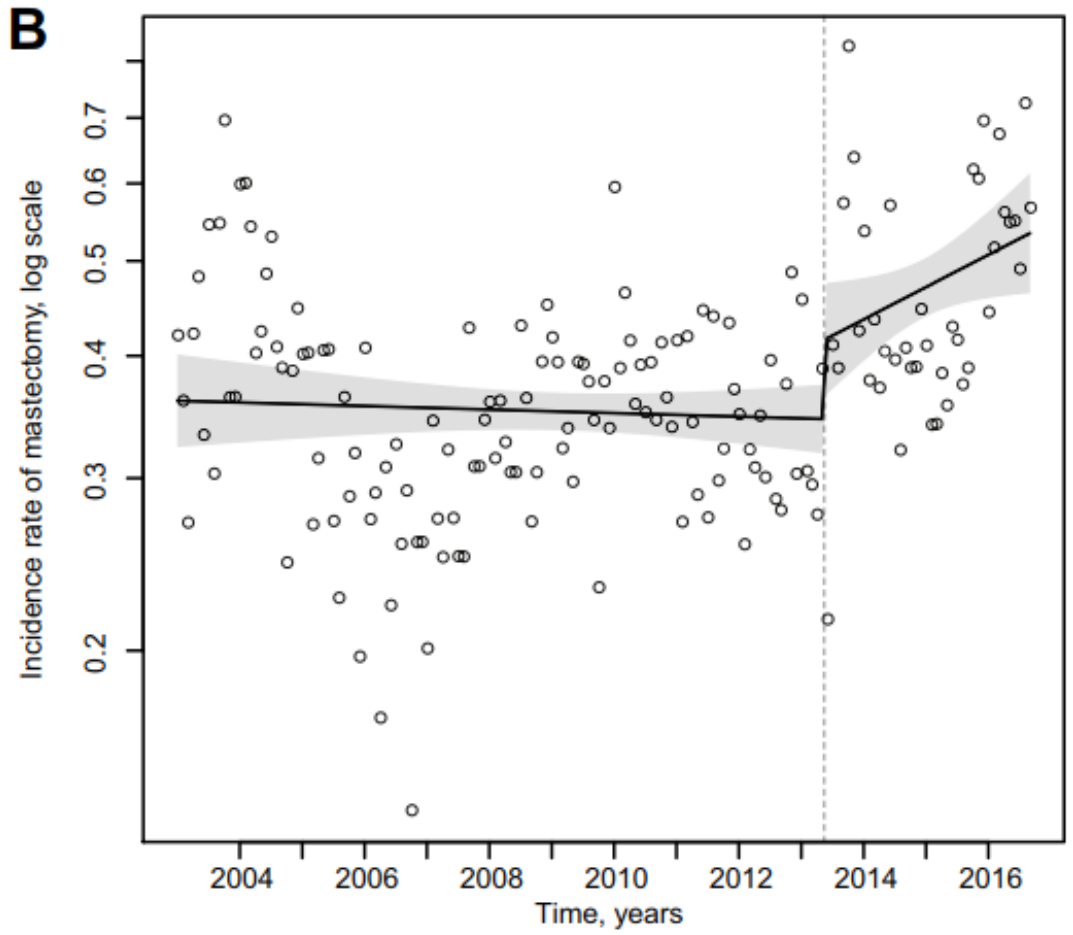
The Angelina Jolie Effect

- **Risk Reduction Mastectomy rate**
  - Initially not observed
  - Long term effect: Upward trend of BRRM 6 months after the news
  - Effect not only on BRCA mutation carriers but also non carriers

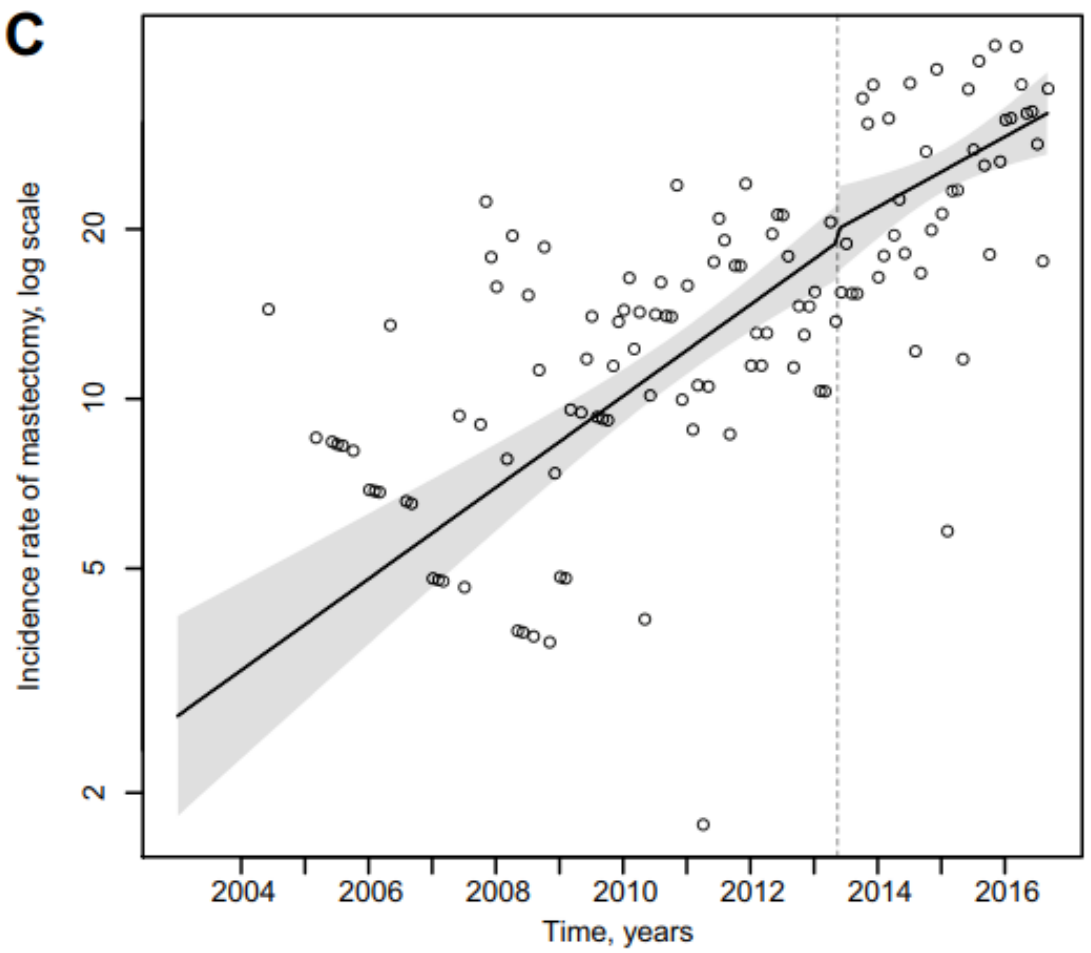
- **Risk Reduction Salpingo-oophorectomy rate**
  - Reported increased rate in BRCA mutation carriers with breast cancer

Lee J et al. J Breast cancer 2017; 20(2):203-207
Evans G. Breast Cancer Research 2015;17:143
Liede A. Breast Cancer Research and Treatment 2018;171:435-442

RRM in Non BRCA tested vs. BRCA tested individuals- unaffected carriers



NO BRCA testing



BRCA testing

Liede at al Breast Cancer Research and Treatment (2018) 171:435-442

Additional lesion detected by MRI scan

- MRI can reveal additional cancers that are occult on mammography (MMG) or ultrasonography (USG) in a median of 16% of patients (1,2)

- Examples:
  - New satellite lesion next to known breast primary
  - New contralateral breast lesion which is otherwise USG occult
  - Abnormal non-mass enhancement around the known primary

Increased mastectomy rate

1. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA 2012;307:1394–1404.
2. Lee SH, Kim SM, Jang M, Yun BL, Kang E, Kim SW, et al. Role of second-look ultrasound examinations for MR-detected lesions in patients with breast cancer. Ultraschall Med 2015;36:140–148.

Reasons for increase of Bilateral/ Contralateral Prophylactic Mastectomy

Increase availability of genetic testing

Increase use of MRI Breasts

Increase internet and media information hence increase public awareness of breast cancer risk

Increase options of Mastectomy techniques

Increase options of Reconstructive techniques

The ability of achieving better and more acceptable cosmetic outcomes and better achievement of symmetry

The RISK ESTIMATION

A Survey Conducted in 2572 adults after the Angelina Jolie News

Awareness of the news

Knowledge of BRCA breast cancer risk

Perception of own risk

Attitude towards her decision

Found

Most participants have

A poor understanding of breast cancer

A poor understanding of risk related to BRCA mutation

Awareness of the Angelina Jolie story was not associated with improved understanding or knowledge

Borzekowski D et al Genetics in Medicine Dec 2013

Characteristics of women who choose prophylactic mastectomy

For BPM

- Fear of cancer
- Wants maximum risk reduction
- Lower desire for additional donor site scar

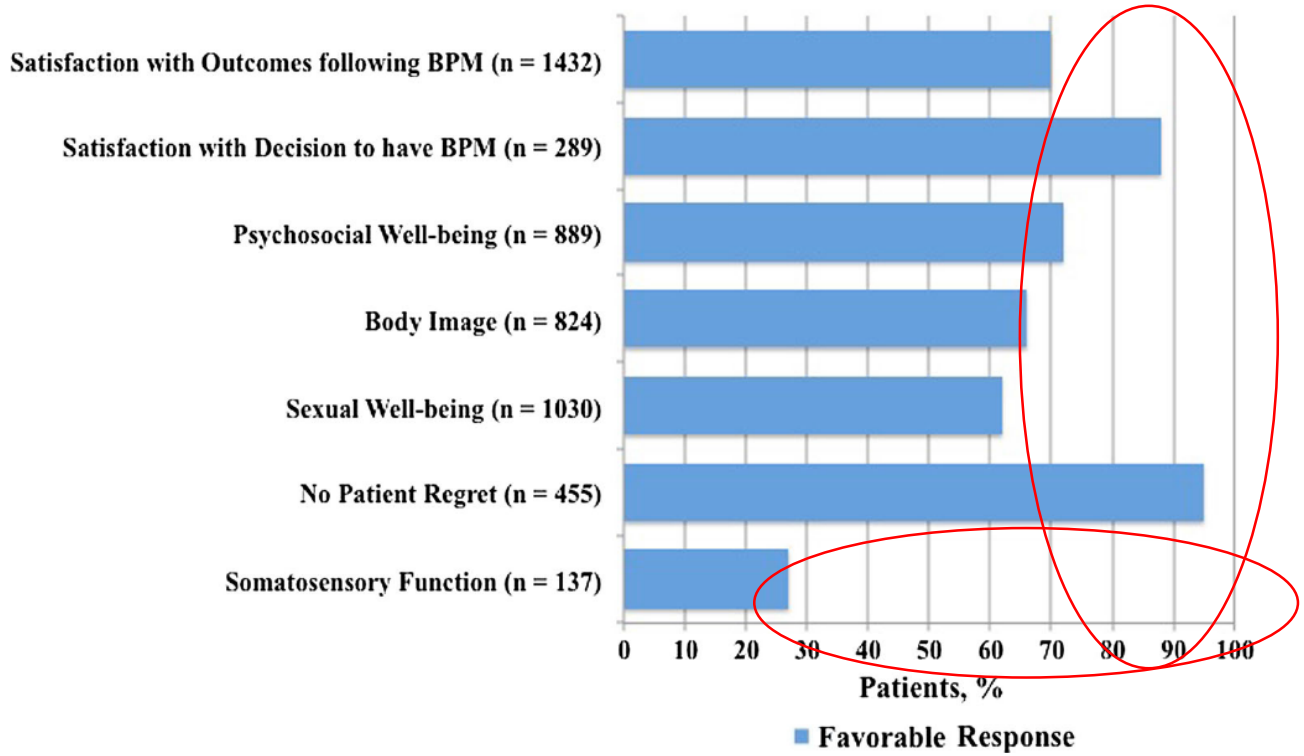
For CPM

- Reduce Recurrence
- Improve Survival
- Achieve Symmetry with reconstruction

- Overestimation of breast cancer risk
- Avoid intensive surveillance and biopsies
- Personal experience of family and friends who have “ lived with cancer”

Majority but NOT ALL Patients Report Favorable Outcomes Following Bilateral Prophylactic Mastectomy

- MASTECTOMY IS NOT REVERSIBLE!
- NOT ALL are completely satisfied with Bilateral Prophylactic mastectomy
- There are also studies which have found some women who have regrets or expressed dissatisfaction



Razdan et al. Qual Life Res 2016; 25:1409
Braude L et al. Patient Educ Couns 2017Dec; 100(12):2181-2189

Reconstruction – a complete perfect revelation!

- Not really….
- Systemic Review looked at two aspects
  - Body image disturbance
  - Quality of life in patients following mastectomy and breast reconstruction

Ominiyi etc International Journal of Science and Research. Vol 3 Issue 11 , Nov 2014

- All studies found mastectomy and breast reconstruction significantly affect negatively on body image and identity
- Can have poor self esteem and self concept, feeling of inferiority
- Poorer quality of life in more advanced stage of breast cancer
- Pain occurred in majority of participants which affects quality of life
- And there are complications even if implant alone is used
  - Flap necrosis, nipple areolar complex necrosis, infection, loss of NAC sensation

Ominiyi etc International Journal of Science and Research. Vol 3 Issue 11 , Nov 2014

The Best with have are for breast cancer patients who decide for Contralateral Prophylactic Mastectomy (CPM)

- CPM reduced the incidence of contralateral breast cancer by more than 90%- 95%
- No Randomised study on survival benefits
  - Future studies unlikely
- Some studies have shown disease free survival benefits but when adjusted to patient, tumor , facility factors , benefits decreased
- Most studies retrospective, biased
- Cochrane review shows no survival benefits

McDonnell SK, Schaid DJ, Myers JL, et al.: Efficacy ofcontralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol 2001;19:3938–3943.
Lostumbo L, Carbine NE, Wallace J: Prophylactic mastectomy forthe prevention of breast cancer. Cochrane Database Syst Rev 2010;CD002748.
Yao et al International Journal of Women's Health 2016: 8

WHAT ARE THE ACTUAL EXISITNG GUIDELINES

Guidelines		NCCN	ACOG	USPSTF	ESMO	NICE	NBOCC, Cancer Australia
Countries		USA			Europe	UK	Australia
RRM	**BRCA1**	Optional, discuss with patient regarding degree of protection, reconstruction options, and risks; consider the family history and residual breast cancer risk with age and life expectancy		Recommended	Consider	For high-risk patients. Should have genetic counseling before surgery, discuss with patients about risk factors, family history, psychosocial & sexual consequences, and reconstruction options	For high-risk patient
	BRCA2						-
	TP53						-
	PTEN						-
	PALB2				-		-
	CDH1				-		-
	ATM						
	CHEK2						
RRSO	***BRCA1***	*35-40y*		*Recommended*	*35-40y*	*For high-risk patient If family completed, Should have genetic counseling before surgery, discuss with patients about risk, family history, effect of early menopause, and psychosocial & sexual consequences*	*For high-risk patient Around 40y*
	BRCA2	*40-45y*			*40-49y*		
	PTEN	-			*Risk-reducing hysterectomy*		-
	BRIP1	*45-50y*			*45y*		-
	RAD51C						-
	RAD51D						-

RRM = Risk-reducing mastectomy
RRSO = Risk-reducing salpingo-oophorectomy

AND

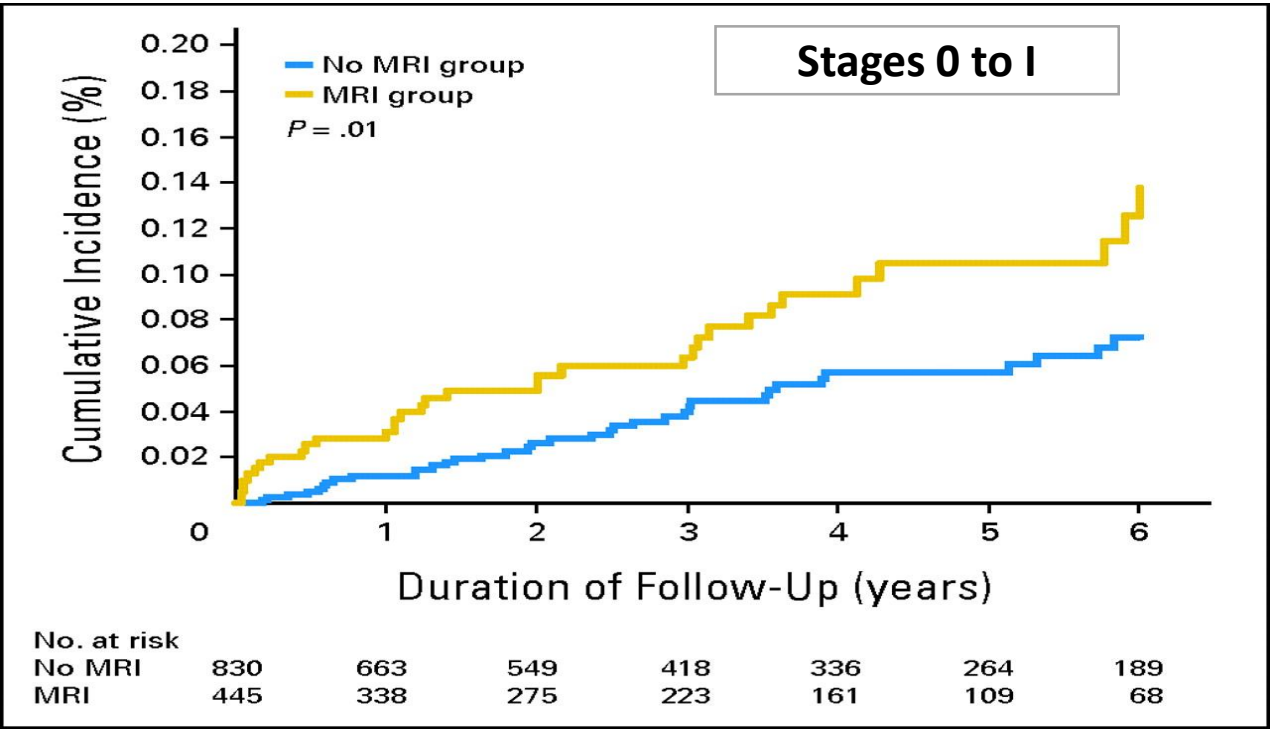
There Are OTHER OPTIONS !

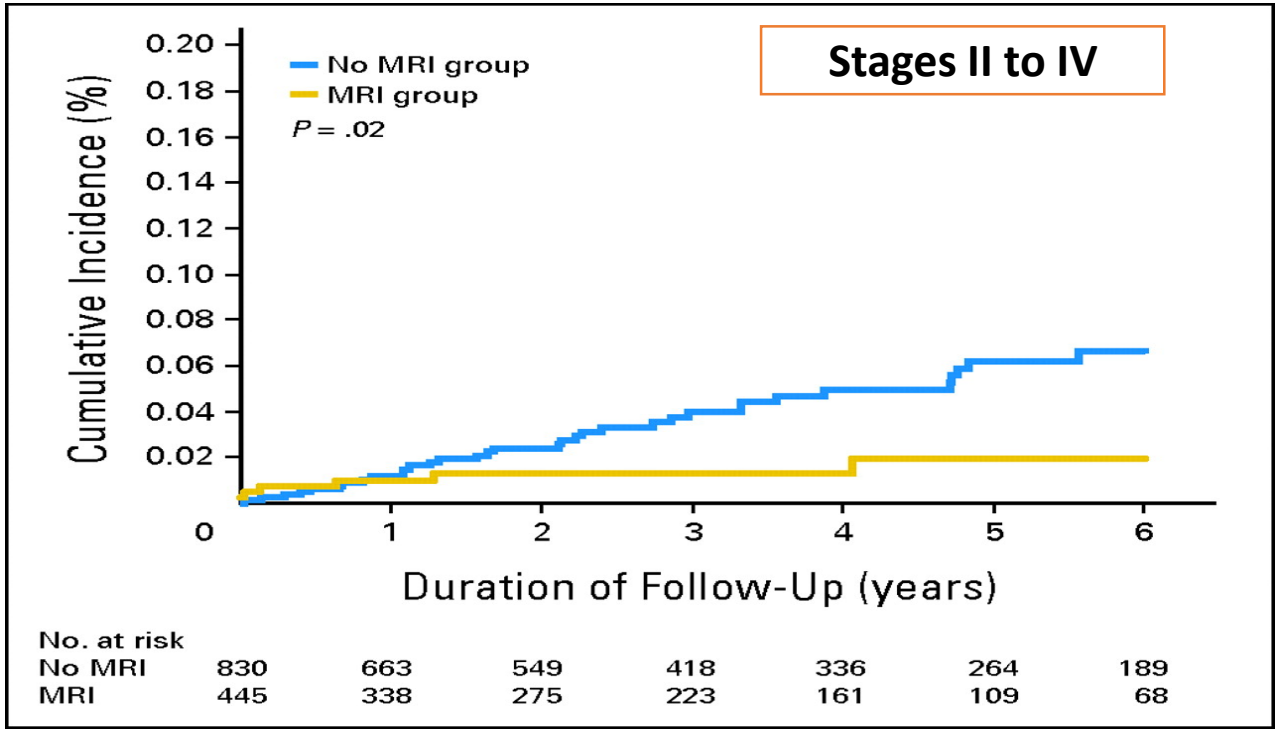
HIGH RISK BREAST SURVEILLANCE

FOR EARLY DIAGNOSIS

Annual MRI surveillance reduced incidence of advanced-stage breast cancer in *BRCA1*/2 carriers

Cumulative incidence of early-/ late-stages of breast cancer





Cumulative incidence at Year 6

- MRI screened cohort: 13.8% (95% CI, 9.1% - 18.5%)
- No MRI control group: 7.2% (95% CI, 4.5% - 9.9%)

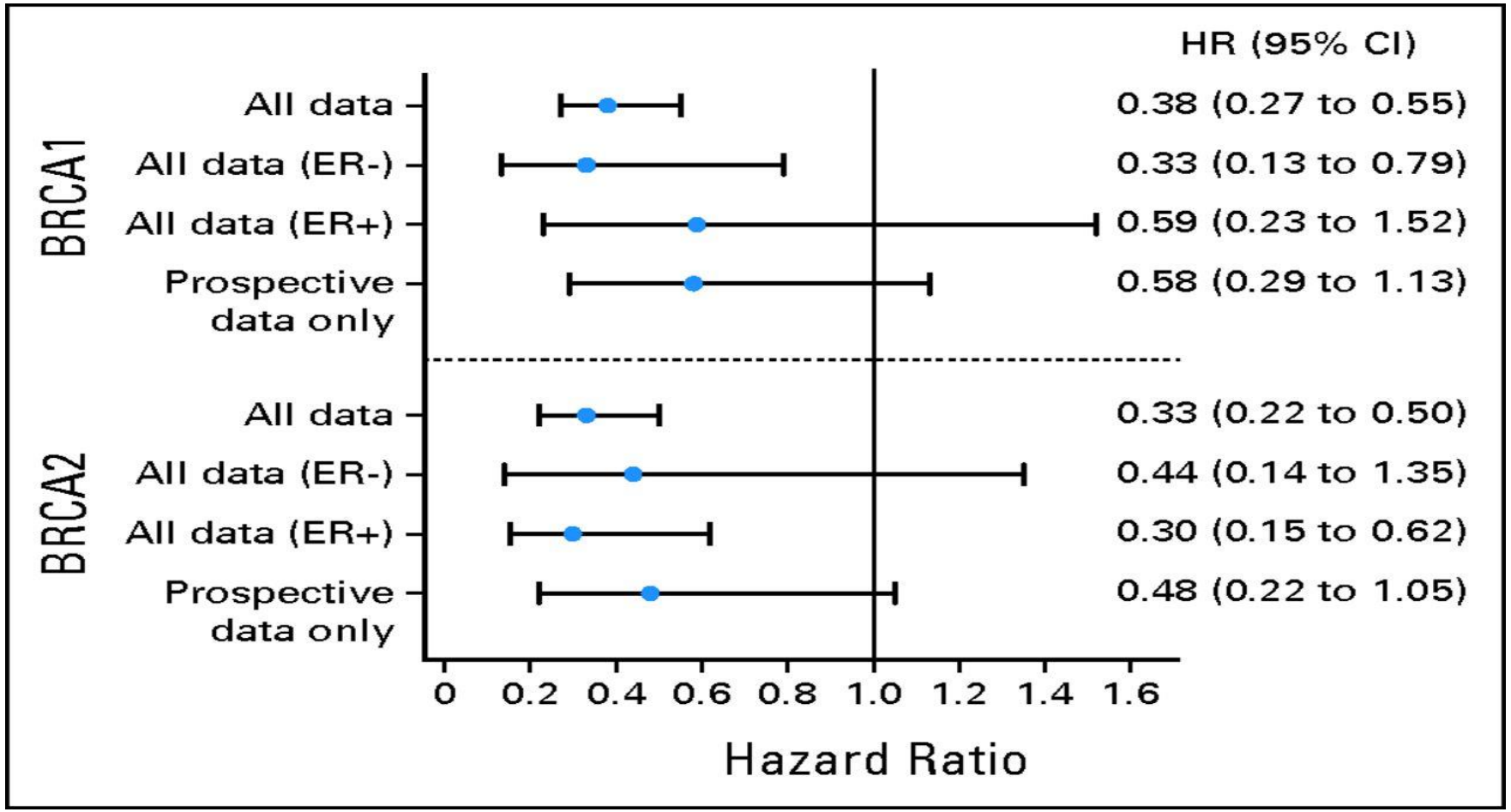
Cumulative incidence at Year 6

- MRI screened cohort: 1.9% (95% CI, 0.2% - 3.7%)
- No MRI control group: 6.6% (95% CI, 3.8% - 9.3%)

Warner *et al.*, 2011

Non Surgical and alternative Surgical Prevention

Hazard ratio estimates for risk of contralateral breast cancer associated with tamoxifen use by women with BRCA1 and BRCA2 mutations

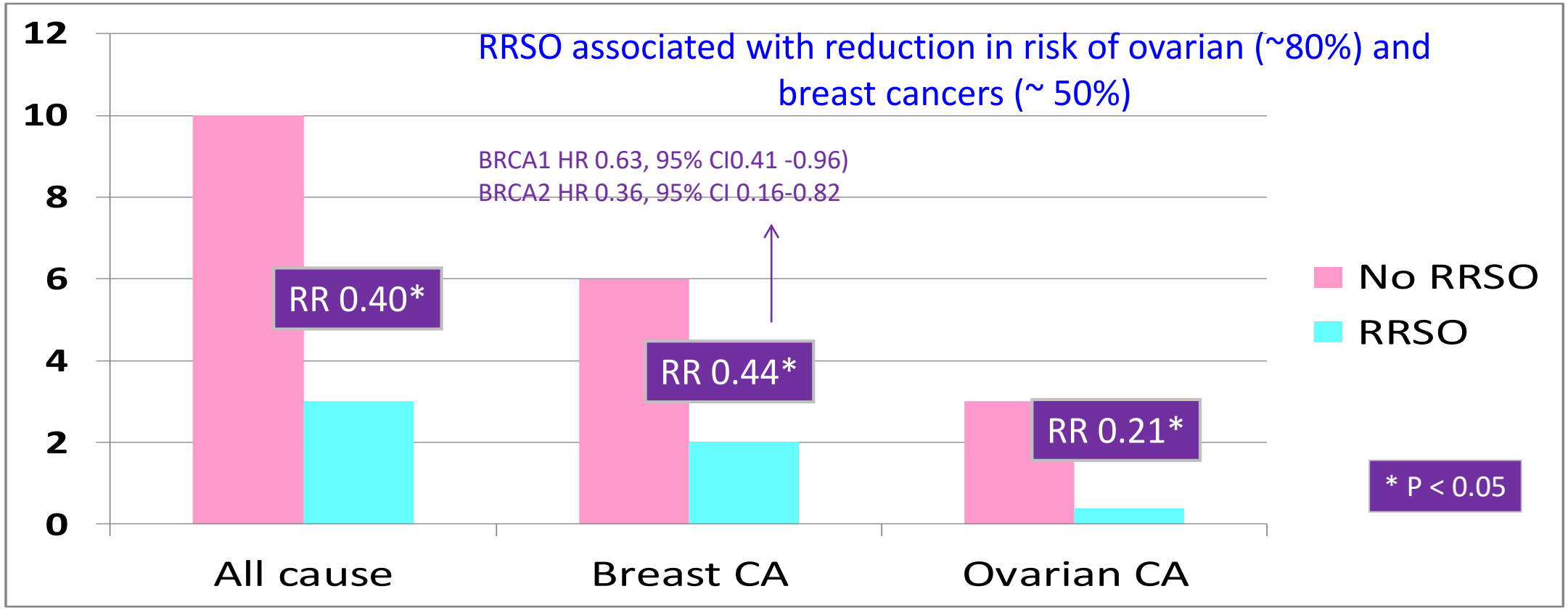


When ER status known, BRCA1 26% ER+ and BRCA2 77% ER+

Phillips K et al. JCO 2013;31:3091-3099

Courtesy of Dr. JE Garber

Risk Reducing Salpingo-Oophorectomy (RRSO)
Mortality Reduction in BRCA Carriers



Domchek S et al. JAMA 2010;304:967

- With a similar survival rate between BCS vs Mastectomy
- Lack of Randomized Controlled Trials to support Risk Reduction Mastectomy or Contralateral Prophylactic Mastectomy
- A possible misleading Risk Interpretation
- Presence of options other than Surgical (breast) Prevention
- Better adjuvant treatment
- Risk of Complications
- Social media publication bias
- Psychological Consequences
- Irreversibility of the Surgical Procedure

I do not support that
A BRCA mutation carrier with early breast cancer should have mastectomy be it unilateral or bilateral

Thank you for supporting

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