Risk Reducing Surgery

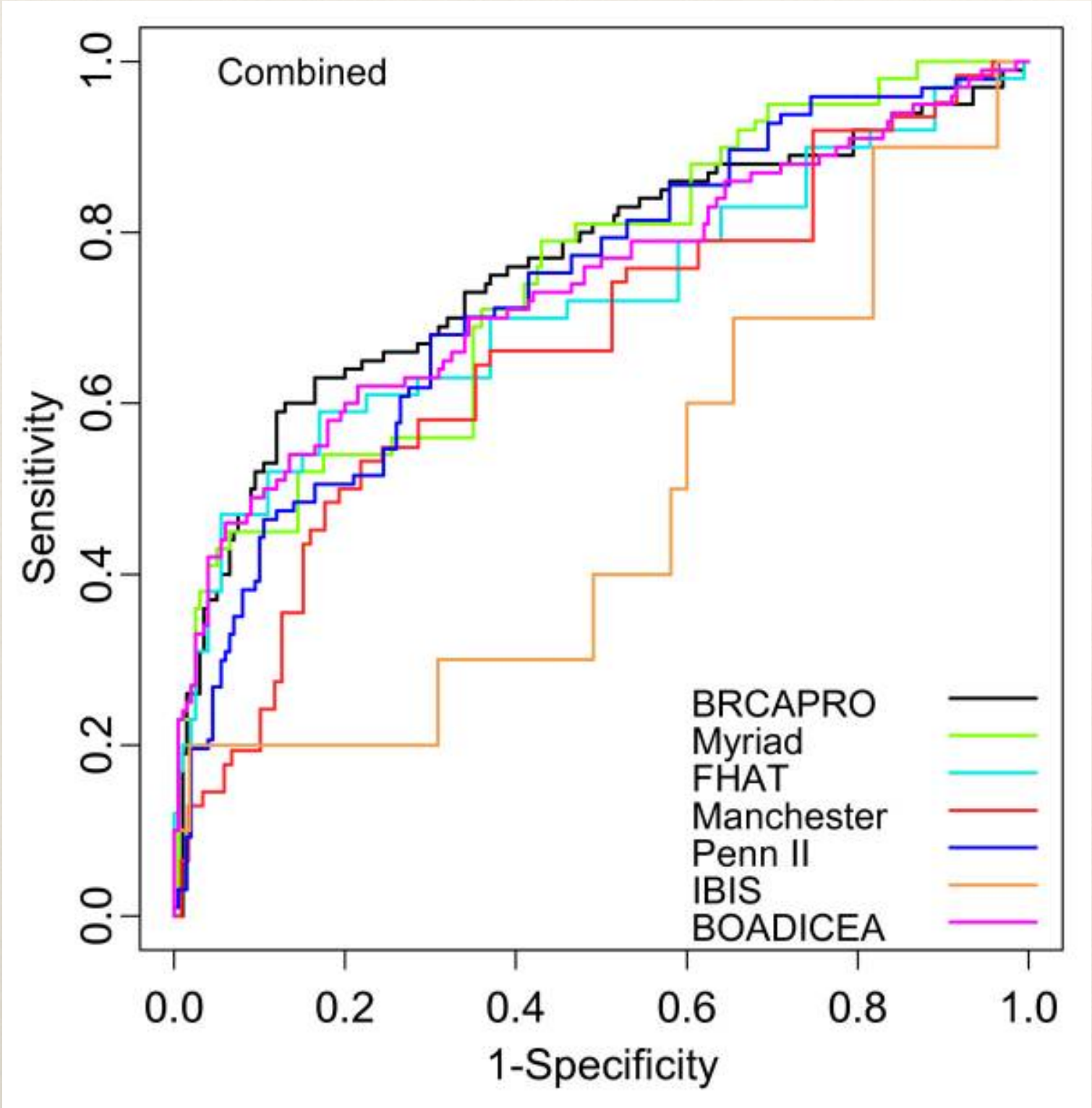
UK guidelines/Surgical techniques

Symposium on risk reducing mastectomies and reconstruction
Swedish Surgical Week 2018

Kristjan S. Asgeirsson
Consultant Oncoplastic Breast Surgeon
Nottingham Breast Institute/Nordic Breast Institute

Modern day genetic counselling and predictive testing

- We are selecting patients for BRCA genetic testing based on family history
  - 10-20% rule, Manchester score of >17
- Patients can have a strong family history and do not have a BRCA mutation
- Patients without any family history can have a BRCA mutation


Combined
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
BRCAPRO
Myriad
FHAT
Manchester
Penn II
IBIS
BOADICEA

OXFORD

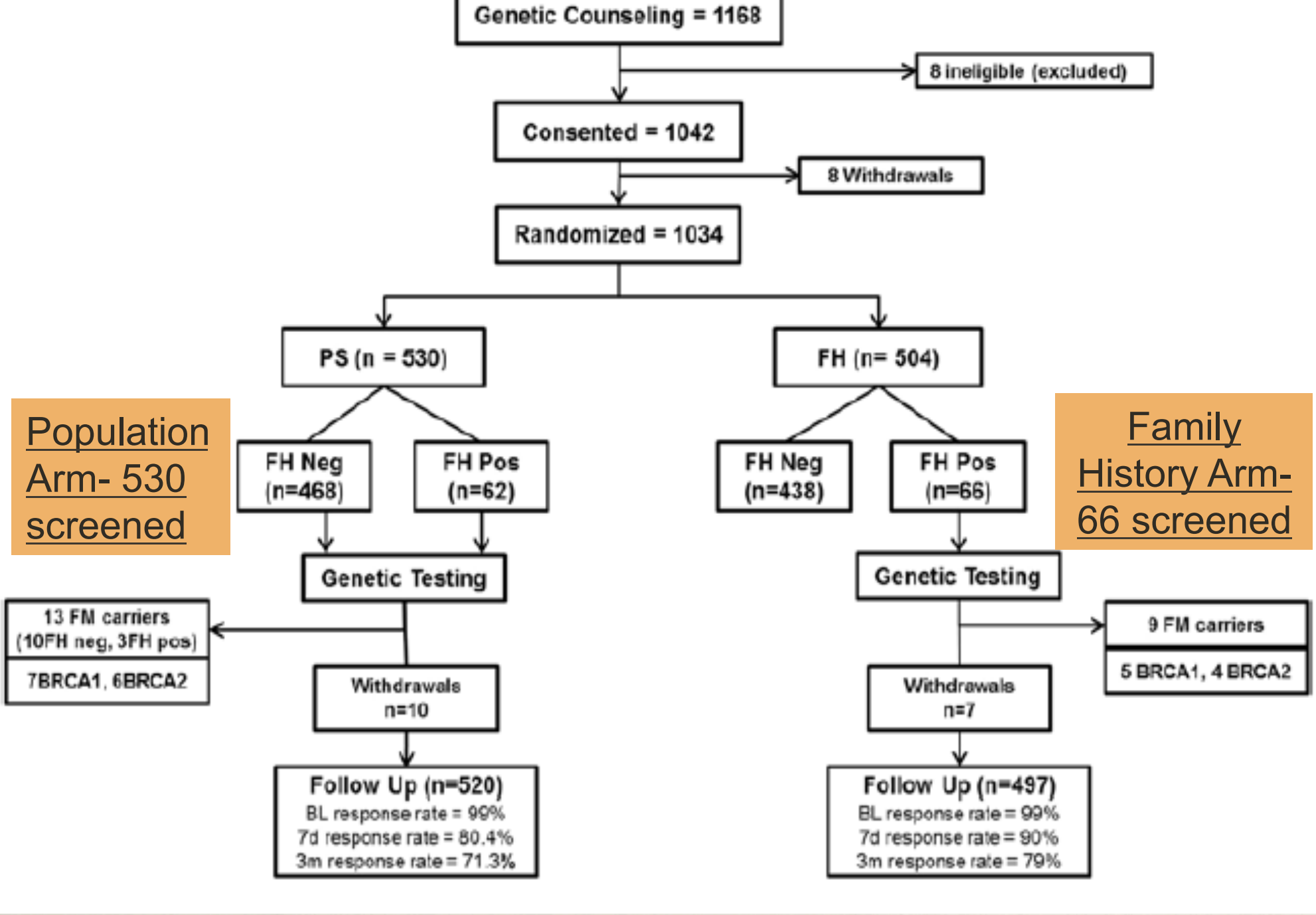
JNCI J Natl Cancer Inst (2015) 107(1): dju379

doi:10.1093/jnci/dju379
First published online November 30, 2014
Article

ARTICLE

Population Testing for Cancer Predisposing BRCA1/BRCA2 Mutations in the Ashkenazi-Jewish Community: A Randomized Controlled Trial

Ranjit Manchanda, Kelly Loggenberg, Saskia Sanderson, Matthew Burnell, Jane Wardle, Sue Gessler, Lucy Side, Nyala Balogun, Rakshit Desai, Ajith Kumar, Huw Dorkins, Yvonne Wallis, Cyril Chapman, Rohan Taylor, Chris Jacobs, Ian Tomlinson, Alistair McGuire, Uziel Beller, Usha Menon, Ian Jacobs


Genetic Counseling = 1168
8 ineligible (excluded)
Consented = 1042
8 Withdrawals
Randomized = 1034
PS (n = 530)
FH (n= 504)
Population Arm- 530 screened
FH Neg (n=468)
FH Pos (n=62)
FH Neg (n=438)
FH Pos (n=66)
Family History Arm- 66 screened
Genetic Testing
Genetic Testing
13 FM carriers (10FH neg, 3FH pos)
7BRCA1, 6BRCA2
Withdrawals n=10
9 FM carriers
5 BRCA1, 4 BRCA2
Withdrawals n=7
Follow Up (n=520)
BL response rate = 99%
7d response rate = 80.4%
3m response rate = 71.3%
Follow Up (n=497)
BL response rate = 99%
7d response rate = 90%
3m response rate = 79%

	Population Screening Arm (N=530)	Family History Arm (N=504)
Overall BRCA positivity	2.45%	
Percentage of FH BRCA carriers	1.16% (12/1034)	
Genetic testing	530 (all)	66 (fulfill FH criteria)
No. of carriers detected (during study)	13/530	9/66
BRCA + with FH	3/13	9/66
BRCA + without FH (2.04%)	10/13	Additional 5 (detected after study 3 yr completion in 210 participants)
Number of BRCA carriers not fulfilling FH criteria (of total PS population)	10/530 (1.89%)	5/504 (remaining 218 not tested yet)
No. of BRCA carriers fulfilling FH criteria	3/530	9/504
Sensitivity of approach	Approaching 100%	**44.4%**

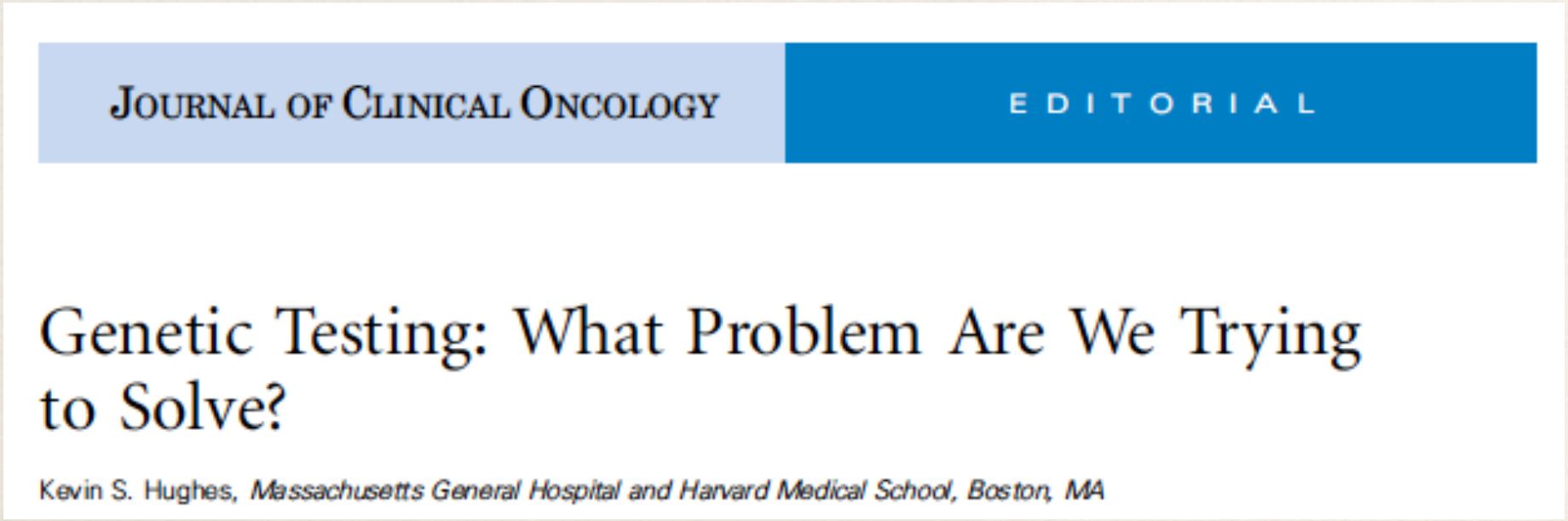
	Population Screening Arm (N=530)	Family History Arm (N=504)
Overall BRCA positivity	2.45%	
Percentage of FH BRCA carriers	1.16% (12/1034)	
		study 3 yr completion in 210 participants)
Number of BRCA carriers not fulfilling FH criteria (of total PS population)	10/530 (1.89%)	5/504 (remaining 218 not tested yet)
No. of BRCA carriers fulfilling FH criteria	3/530	9/504
Sensitivity of approach	Approaching 100%	**44.4%**

56% of carriers would not have been identified if FH criteria were applied to select for testing

Table 5. Mean HADS, SF12, HAI, and MICRA scores at baseline, 7 days and 3 months follow up by group*

Mean score	FH (n = 504)	PS (n = 530)
HADS		
HADS total BL (SD)	9.1 (5.3)	8.8 (5.25)
HADS total 7 d (SD)	9.64 (5.04)	7.59 (5.15)
HADS total 3 mo (SD)	9.12 (6.16)	7.3 (5.23)
HADS anxiety BL (SD)	6.16 (3.46)	6.01 (3.61)
HADS anxiety 7 d (SD)	6.04 (3.4)	5.16 (3.42)
HADS anxiety 3 mo (SD)	5.9 (3.72)	4.8 (3.38)
HADS depression BL (SD)	2.94 (2.55)	2.78 (2.45)
HADS depression 7 d (SD)	3.61 (2.76)	2.44 (2.48)
HADS depression 3 mo (SD)	3.22 (3.01)	2.5 (2.55)
SF12 QoL		
SF12 physical scale BL (SD)	49.17 (5.15)	49.22 (5.08)
SF12 physical scale 7 d (SD)	49.13 (5.13)	49.01 (5.11)
SF12 physical scale 3 mo (SD)	48.88 (5.41)	48.83 (5.46)
SF12 mental scale BL (SD)	52.14 (5.44)	52.28 (5.49)
SF12 mental scale 7 d (SD)	52.42 (5.28)	52.55 (5.10)
SF12 mental scale 3 mo (SD)	52.16 (5.08)	52.34 (4.95)
vsHAI		
vsHAI score BL (SD)	3.1 (2.63)	3.08 (2.51)
vsHAI score 7 d (SD)	3.45 (2.72)	3.18 (2.6)
vsHAI score 3 mo (SD)	3.71 (2.61)	2.99 (2.47)
MICRA		
MICRA distress score 7 d (SD)	1.8 (4.43)	0.78 (2.7)
MICRA uncertainty score 7 d (SD)	4.4 (5.97)	2.98 (4.78)
MICRA positive experiences score 7 d (SD)	6.25 (5.49)	6.13 (6.03)
MICRA distress score 3 mo (SD)	1.04 (2.08)	0.59 (2.28)
MICRA uncertainty score 3 mo (SD)	3.71 (4.94)	2.22 (4.39)
MICRA positive experiences score 3 mo (SD)	7.42 (6.81)	9.06 (7.2)

* BL = baseline; FH = family history; HADS = Hospital Anxiety and Depression Scale; HAI = Health Anxiety Inventory; MICRA = Multidimensional Impact of Cancer Risk Assessment Scale; PS = population screening; SD = standard deviation; SF12 QoL = SF12 quality-of-life scale.



- Of all breast and ovarian cancer survivors in the USA eligible for testing
  - **Only 14% were actually tested**
- 90% of unaffected BRCA carriers had yet to be identified and most at risk had yet to be tested

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Genetic Testing: What Problem Are We Trying to Solve?

Kevin S. Hughes, *Massachusetts General Hospital and Harvard Medical School, Boston, MA*

"Is the problem that large numbers of women have had undue levels of stress and anxiety, have not received proper informed consent, or have been managed inappropriately because they were tested by someone other than a genetic counselor? Or is the problem that hundreds of thousands of mutation carriers are still unaware of their status and will develop cancers that could have been prevented or found earlier

So who are we testing???

- Women with breast cancer
  - Triple negative <60
  - Bilateral BC, both <50
  - BC <30
  - BC + OC any age

Failure of cancer prevention

- Cancer is diagnosed in a known BRCA mutation carrier
- Diagnosing a BRCA mutation carrier

  after diagnosis of cancer

Population based genetic testing

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arfgerd.is

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BRCA2 arfgerð

ÍSLENSK ERFÐAGREINING

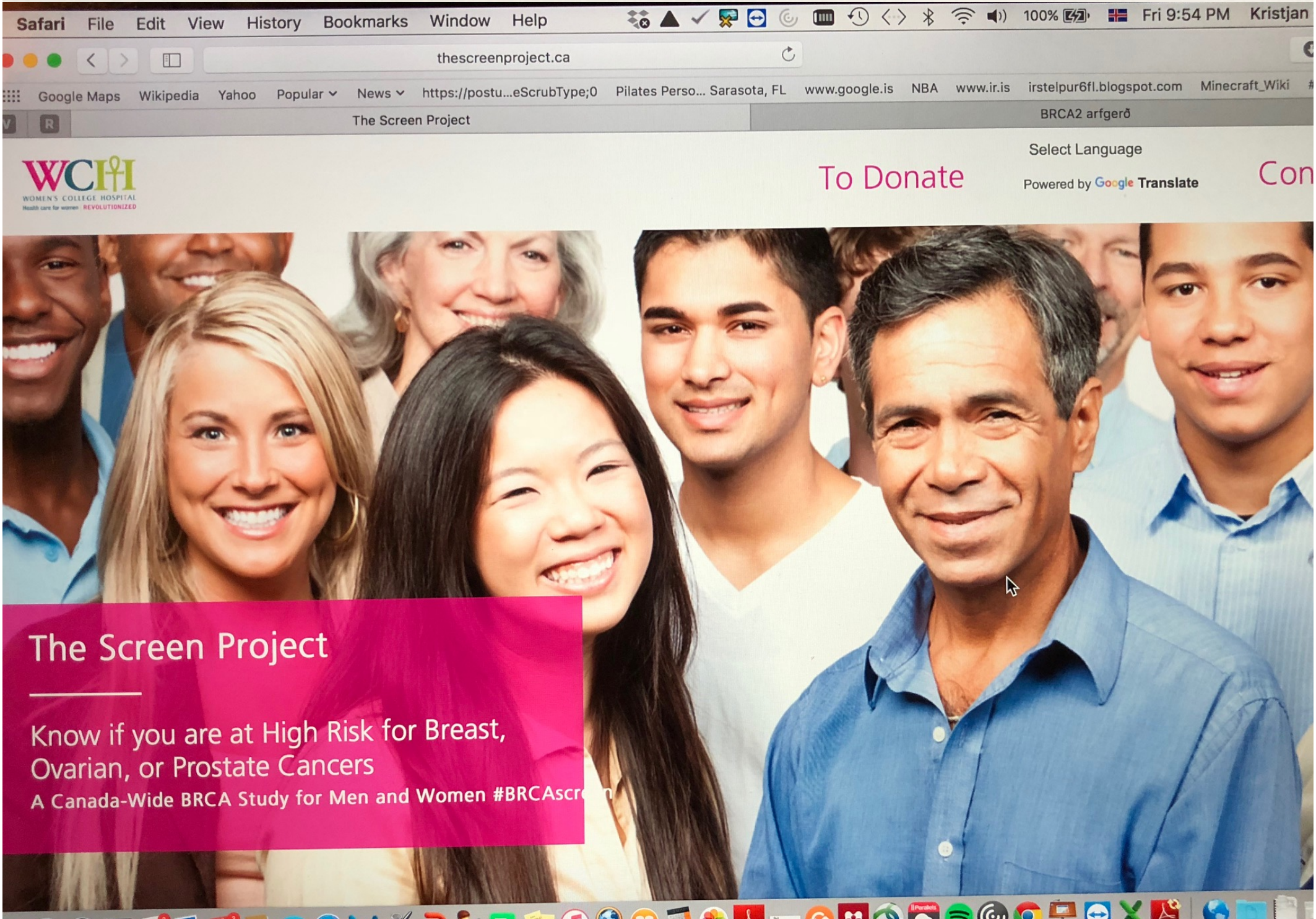
Forsíða Upplýsingar Algengar spurningar Þjónustan Starf okkar

BRCA2 ARFGERÐ

Á þessu vefsvæði geta margir Íslendingar komist að því hvort þeir beri 999del5 erfðabreytuna í BRCA2 geninu sem eykur verulega líkur á krabbameini.

Niðurstöður eru til fyrir flesta einstaklinga sem gefið hafa lífsýni í rannsóknir Íslenskrar erfðagreiningar. Úrvinnsla gagna tekur að minnsta kosti tvær vikur.

Innskráning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BRCA2 arfgerð
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The Screen Project
Know if you are at High Risk for Breast, Ovarian, or Prostate Cancers
A Canada-Wide BRCA Study for Men and Women #BRCAscr


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95 UK pounds
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The Screen
Know if you are at High Risk for Breast, Ovarian, or Prostate Cancers
A Canada-Wide BRCA Study for Men and Women #BRCAscr

Rationale for Population Screening

- No need for pre-test counselling
- No mutation carrier will be left unidentified
- People will know they are mutation carriers before being diagnosed with cancer
- Patients will know their carrier status when diagnosed with cancer, using the information to guide their treatment

Risk reducing surgery

NICE National Institute for Health and Care Excellence

NICE guideline

Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer

Clinical guideline

Published: 25 June 2013

NICE guidelines

- Risk reducing surgery is appropriate **only** for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team
- Women considering bilateral risk-reducing mastectomy should have genetic counselling in a specialist cancer genetic clinic before a decision is made
- Pre-operative counselling about psychosocial and sexual consequences of bilateral risk-reducing mastectomy should be undertaken

HIGH RISK

4 or more Relatives

Four or more close relatives with breast and / or ovarian cancer *.

3 Relatives

Three 1st or 2nd degree relatives with an average age of breast cancer under 60*.

One relative with ovarian cancer **and** two 1st or 2nd degree relatives with breast cancer where the average age for the breast cancer is under 60*.

One male breast cancer at any age **and** 2 female breast cancers with an average age under 60

2 Relatives

One 1st **and** one 1st or 2nd degree relatives with an average age of breast cancer under 50.

One 1st **and** one 1st or 2nd degree relative with ovarian cancer.

One ovarian cancer **and** one 1st or 2nd degree relative with breast cancer under 50*.

One 1st or 2nd degree relative with bilateral breast cancer **and** one 1st or 2nd degree relative with breast cancer under 60* **or** ovarian cancer at any age

One male breast cancer at any age **and** a female breast cancer under 50 or an ovarian cancer at any age

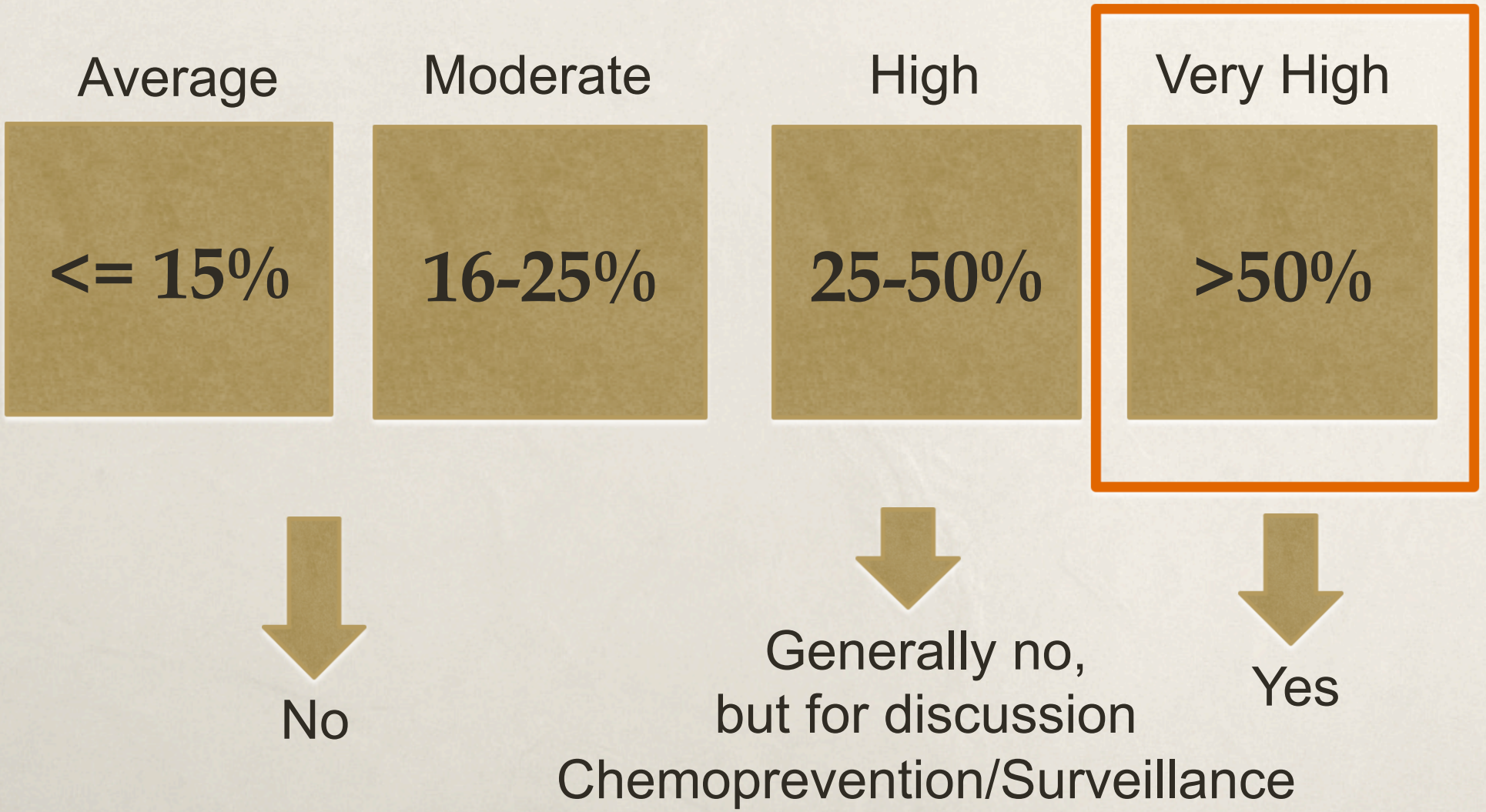
1 Relative

A 1st degree relative with both breast cancer under 50 and ovarian cancer.

A 1st degree relative with bilateral breast cancer, both under 50.

Categories of lifetime risk of breast cancer

- when should we consider risk reducing surgery?

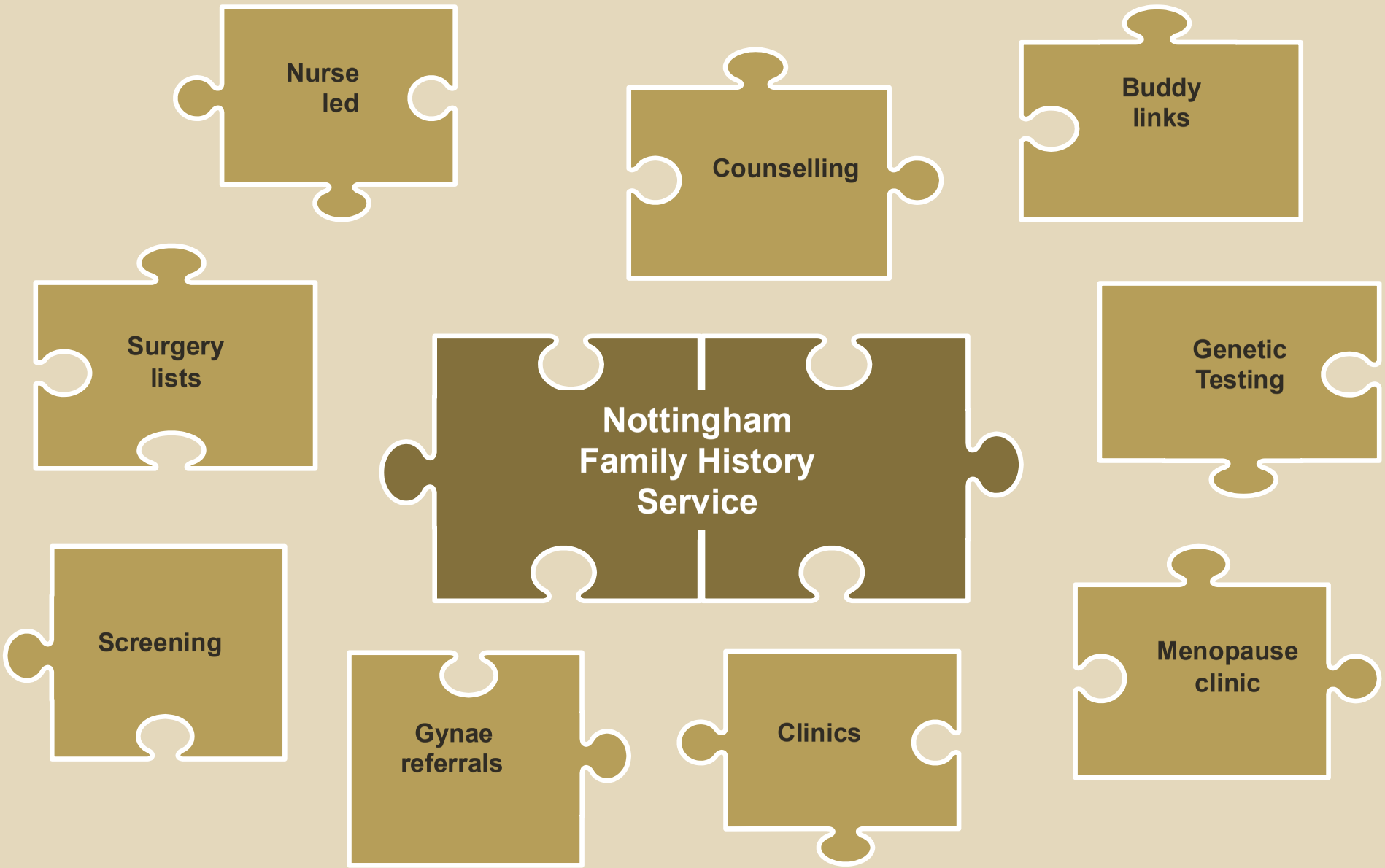


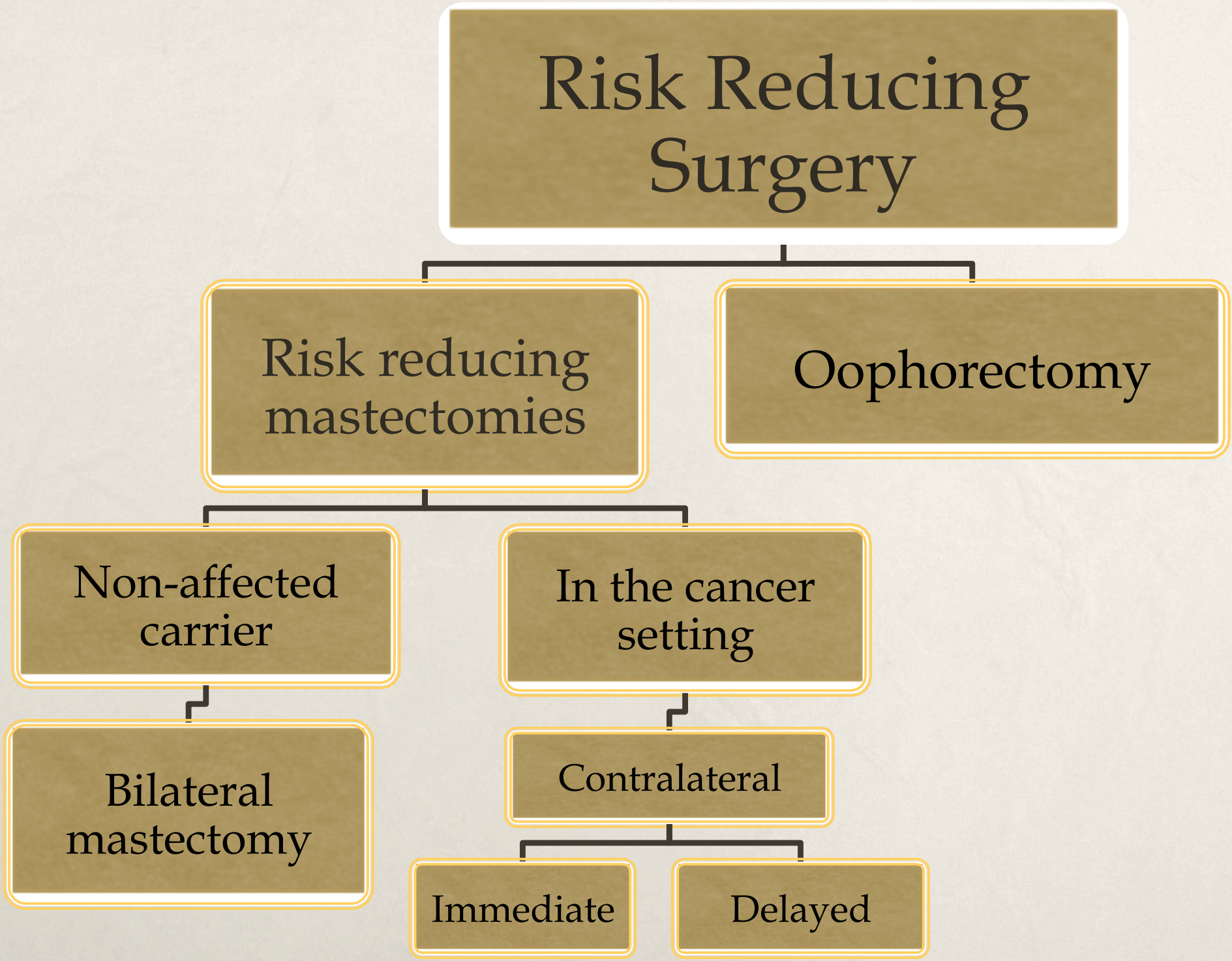
High risk gene mutations

Genetic mutation	Breast cancer risk (%)
CHEK2	20–44
PALB2	33–58
ATM	16–60
CDH1	39–52
TP53	50–85
RAD51C	10–20
PTEN	67–85
STK11	8–45

NICE guidelines

- All women considering bilateral risk-reducing mastectomy should be able to discuss their breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills
- A surgical team with specialist oncoplastic/ breast reconstructive skills should carry out risk-reducing mastectomy and/or reconstruction


Nurse led
Counselling
Buddy links
Surgery lists
Nottingham Family History Service
Genetic Testing
Screening
Gynae referrals
Clinics
Menopause clinic


Risk Reducing Surgery
Risk reducing mastectomies
Oophorectomy
Non-affected carrier
In the cancer setting
Bilateral mastectomy
Contralateral
Immediate
Delayed

What risk are we reducing?

Non-affected

Developing breast cancer

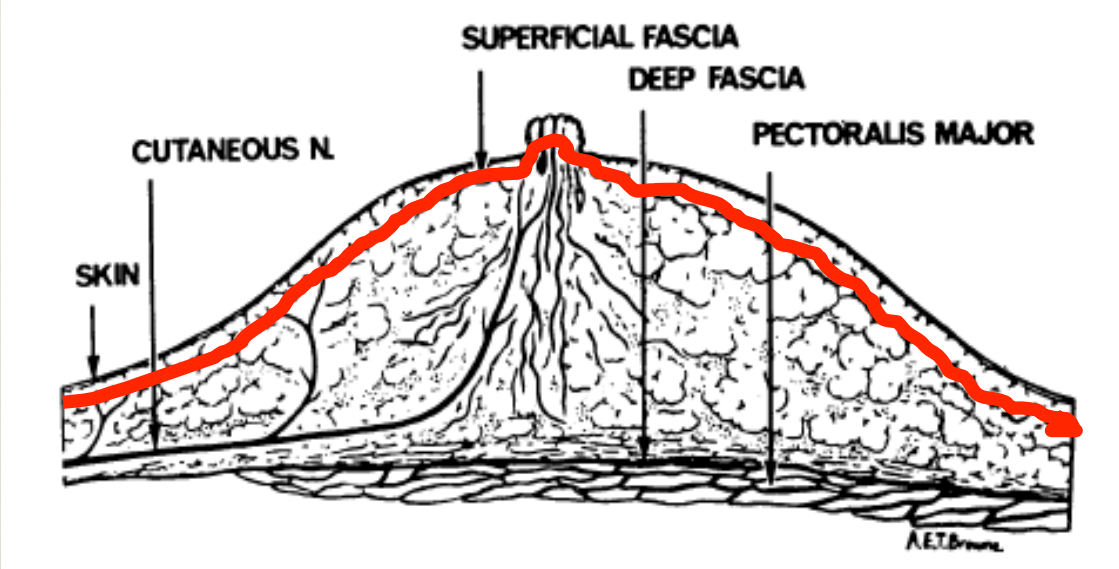
Affected with BC

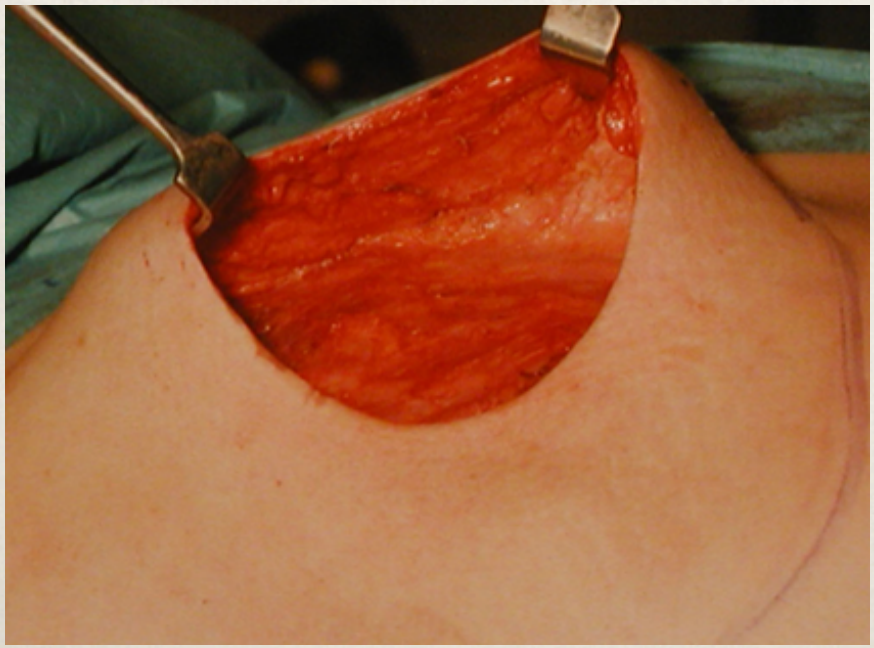
Dying of breast cancer

The approach to risk reducing surgery may be different in the non-affected vs. cancer setting

Risk reducing surgery in the non-affected carrier

How effective is mastectomy at decreasing risk?

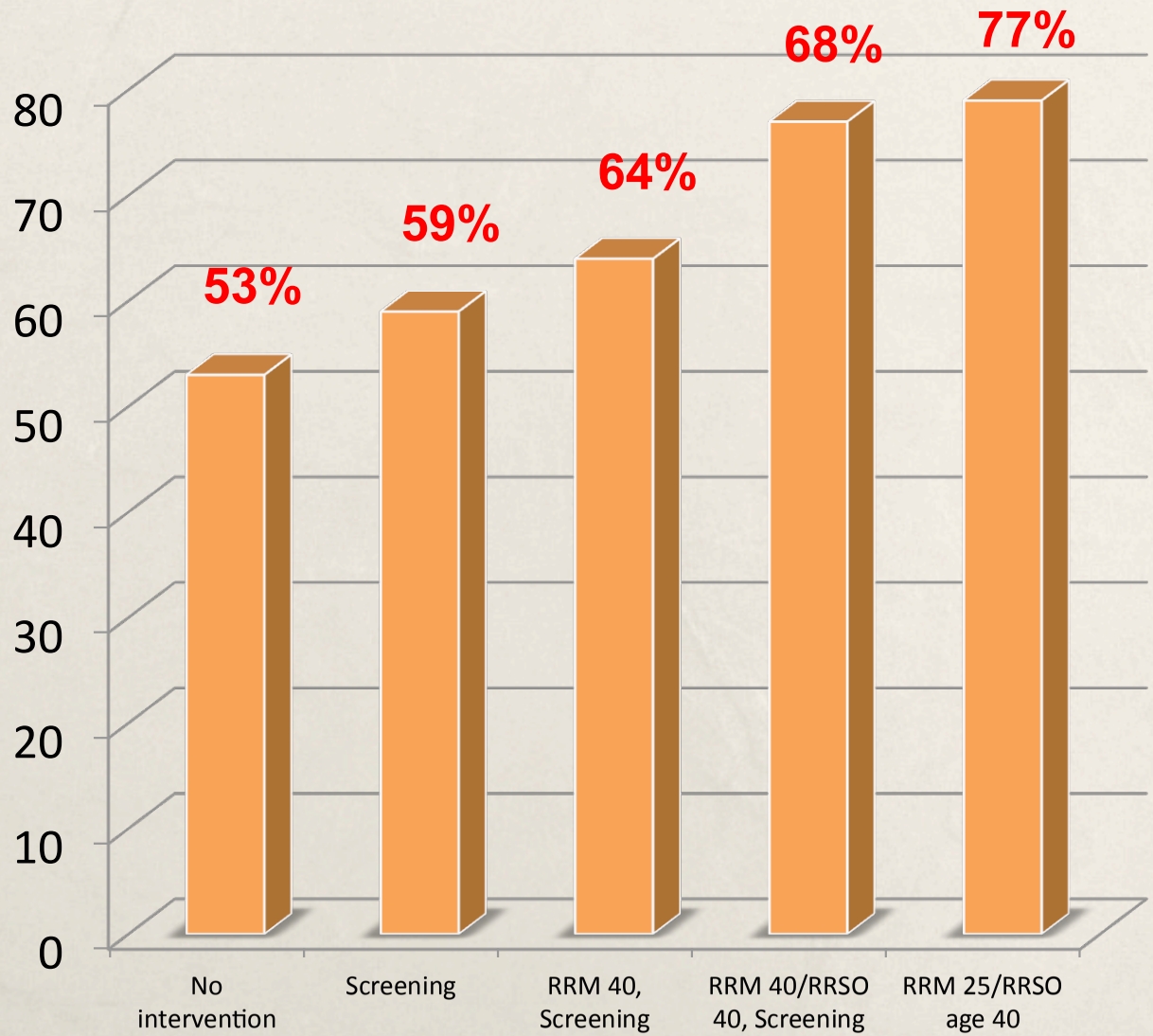




How do you assess the impact of RRM on survival?

- Probability of being alive at a certain age
- Life years gained

Predicted overall survival (%) to age 70 for BRCA1- A model



Kurian et al, J Clin Oncol 2010

Modelling effects of RRM and RRSO on Survival

- BRCA1 – RRSO
  - Most important single intervention to improve survival is RRSO at 40 (15% gain in survival)

Association between oophorectomy and all-cause mortality by mutation status and history of breast cancer

Age group at study entry	N	BRCA1 Hazard ratio (95% CI) P-value	BRCA2 Hazard ratio (95% CI) P-value
Previous Breast Cancer	2565	0.31 (0.24-0.39) <0.0001	0.34 (0.22-0.52) <0.0001
No Previous Cancer	2633	0.21 (0.13-0.36) <0.0001	0.65 (0.07-5.73) 0.70

Narod S, kind permission, JCO 2014

Modelling effects of RRM and RRSO on Survival

- Survival maximized with RRM at 25 and RRSO at 40
- Little survival benefit to RRM if after 40

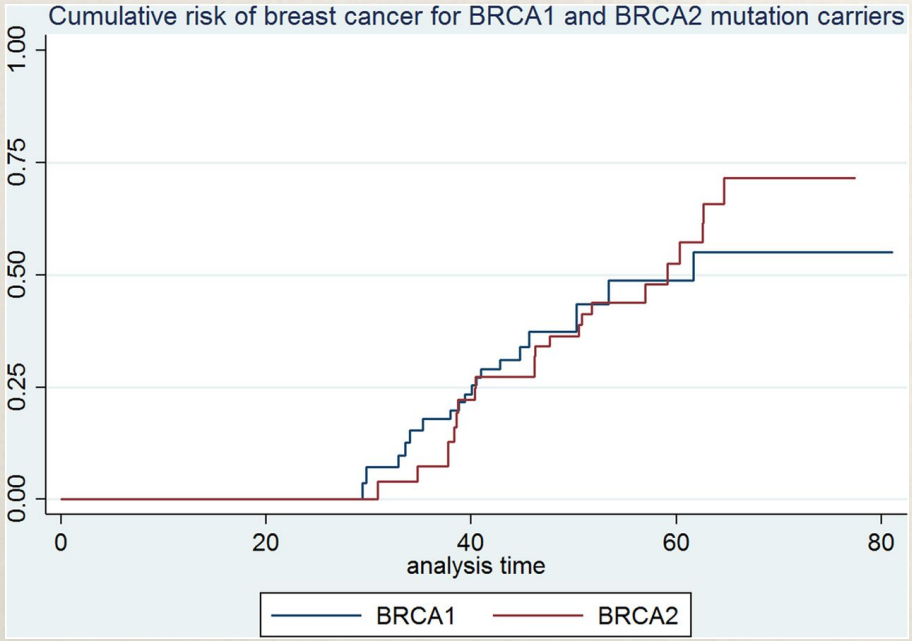
Modelling effects of RRM and RRSO on Survival

- BRCA1 – RRSO
  - Most important single intervention to improve survival is RRSO at 40 (15% gain in survival)
- BRCA2 – RRM
  - Most important single intervention is RRM by age 40 (7% survival gain)
- RRSO+RRM at 40 – better than either alone
  - BRCA1 24% survival gain
  - BRCA2 11% survival gain

For many non-affected women, reducing BC risk and need for BC treatment is still worthwhile even if there is not a survival benefit!

General Recommendation of RRM in the "prophylactic" setting

- RRM ~40 ??
- RSO, 35 for BRCA1/ 45 for BRCA2

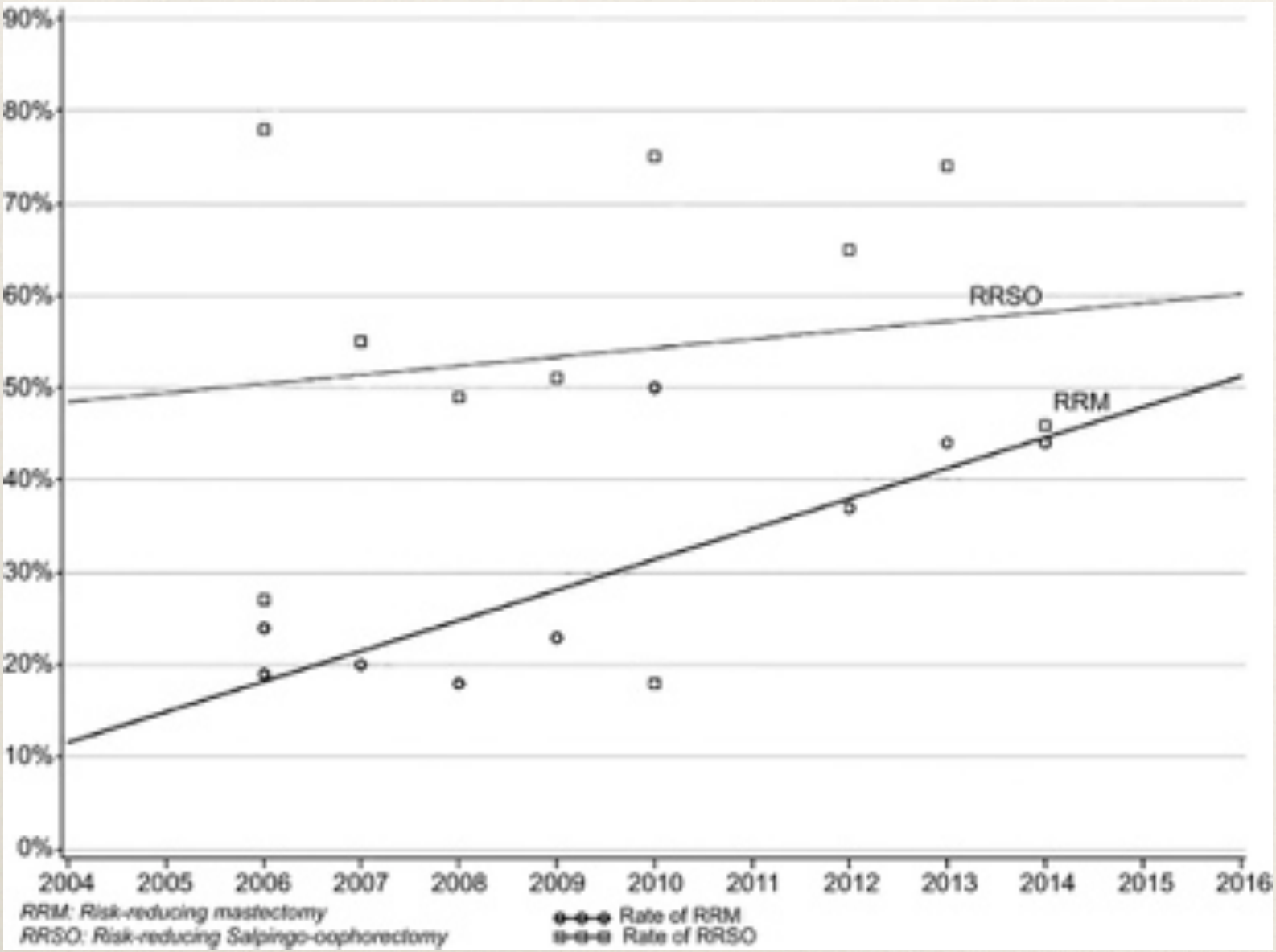


Uptake of RRM in BRCA carriers

Author	Date	Sample Size	%RRM
Uyei et al	2006	37	24
Kram et al	2006	43	19
Friebel et al	2007	537	21
Metcalfe et al	2008	1383	18
Beattle et al	2009	272	23
Kwong et al	2010	31	18
Skytte et al	2010	306	50
Schwartz et al	2012	144	37
Garcia et al	2013	305	44
Filipo et al	2014	87	44

Filippo-Morten et al., Breast J 2016; 22 (1):33-45

Uptake of RRM is increasing



Filippo-Morten et al., Breast J 2016; 22 (1):33-45

Factors driving increased RRM

- Increased awareness and lower cost of genetic testing
- Technical advances in surgery
  - Better access to DIEPs

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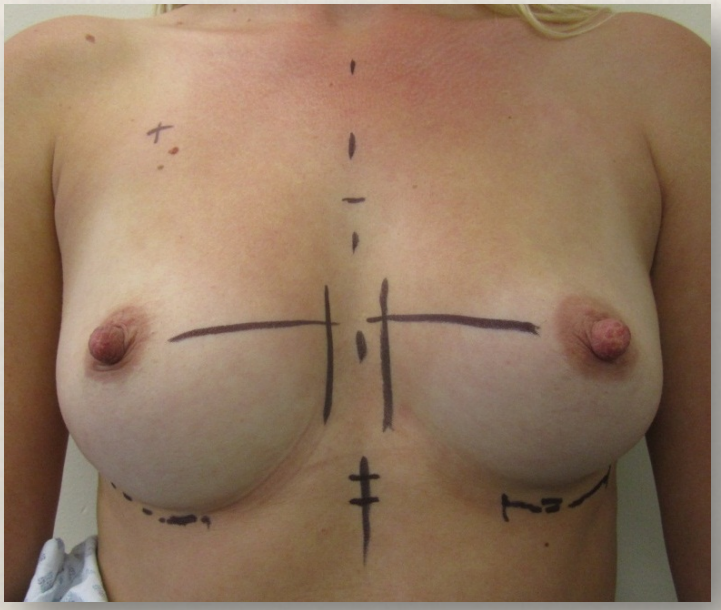
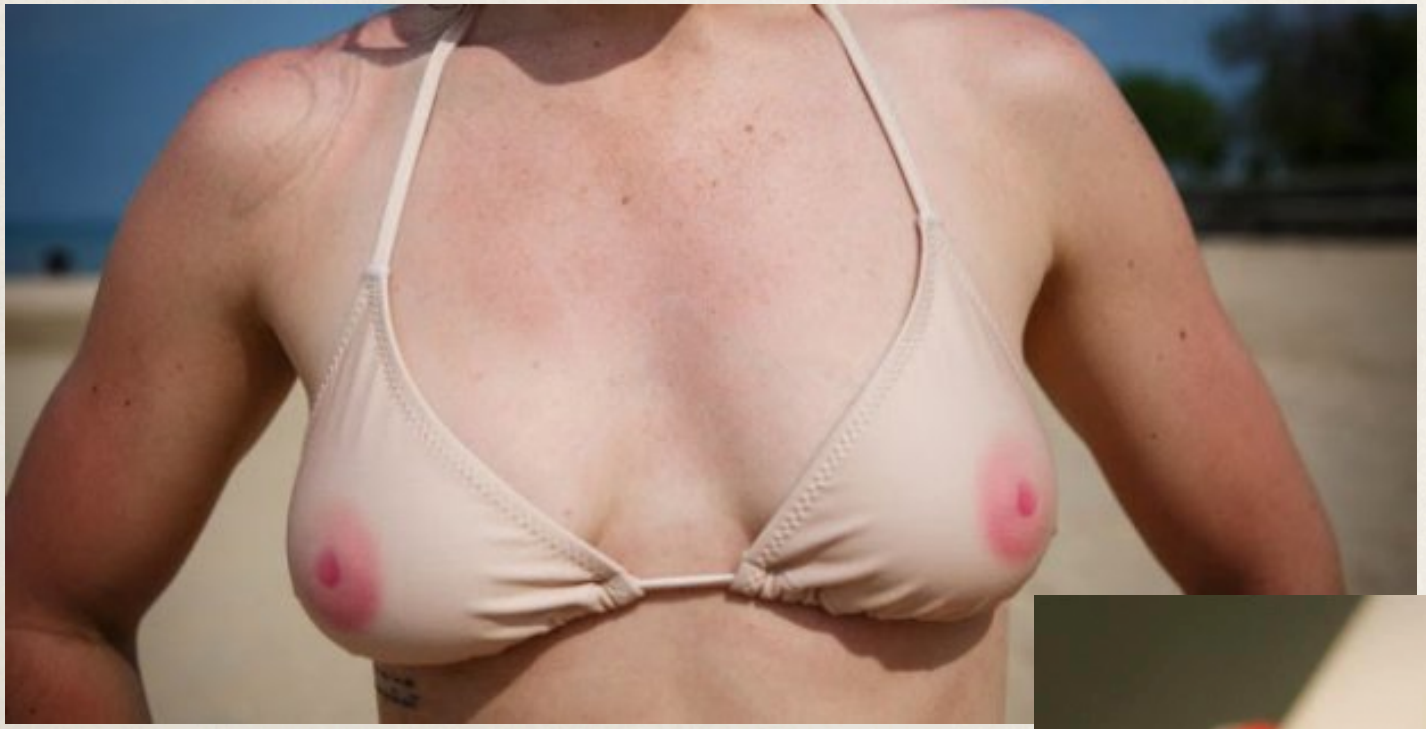
- But of course…..

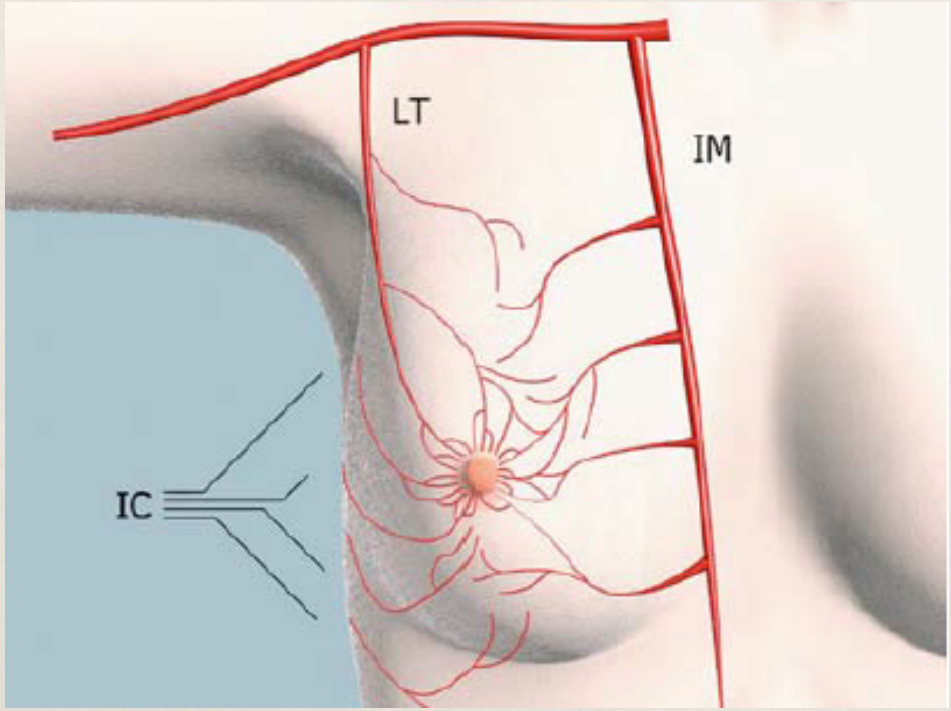
Factors driving increased RRM

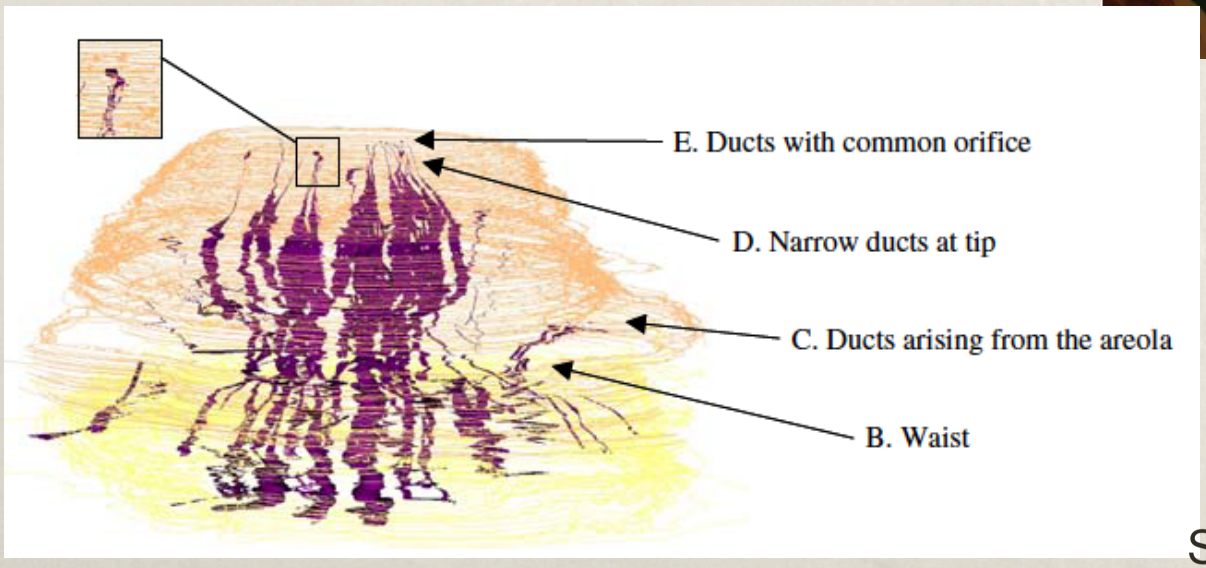
- Increased awareness and lower cost of genetic testing
- Technical advances in surgery
  - Better access to DIEPs
- But of course…..
  - the NSM
  - Pre-pectoral



Nipple sparing mastectomy



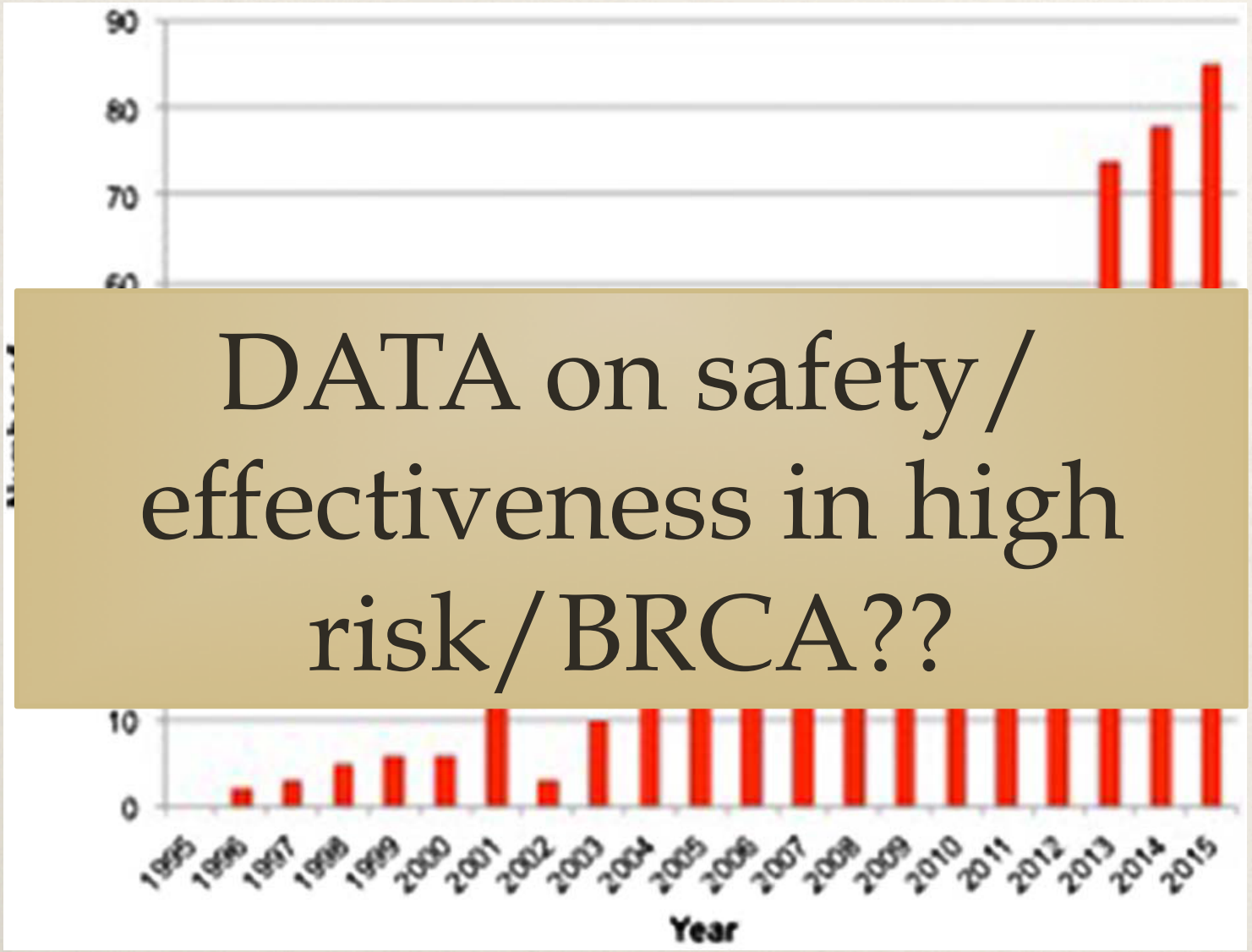




TDLU in 3/32 (9%)
all in base of nipple

Stolier et al, Ann Surg Oncol, 2008

Nipple sparing mastectomy



NSM for Risk Reduction

- No randomized trial data
- Some comparative data in high risk with FH
- Some observational data in BRCA carriers
  - Short-term f/U

NSM for Risk Reduction

- Women with high risk due to FH
  - 639 patients BPM 1960-1993; 14 yr f/u
  - 90% subcutaneous mastectomy

  - Cancers;
    - 6 in flaps
    - 1 in NAC (0.2%)

Hartmann et al, JNCI 2001

Factors driving increased RRM

- Increased awareness and lower cost of genetic testing
- Technical advances in surgery
  - Better access to DIEPs
- But of course….
  - the NSM
  - Pre-pectoral

Risk reducing surgery in the cancer setting

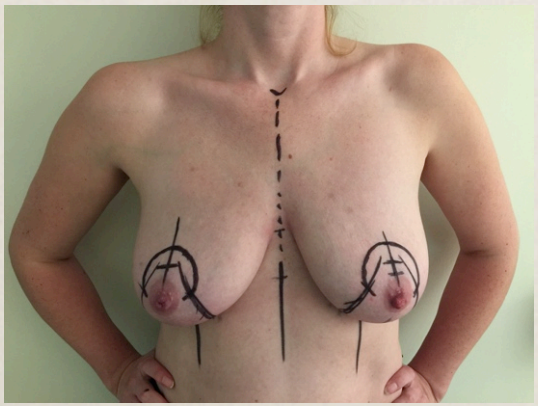
At least in the short term……

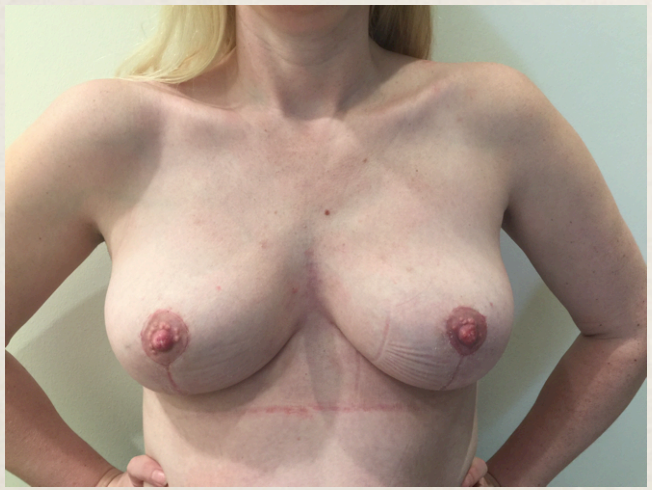
In a BRCA mutation carrier with breast cancer, the risk of dying from breast cancer is related to the disease she has and to a lesser extent to the disease she may get in the future

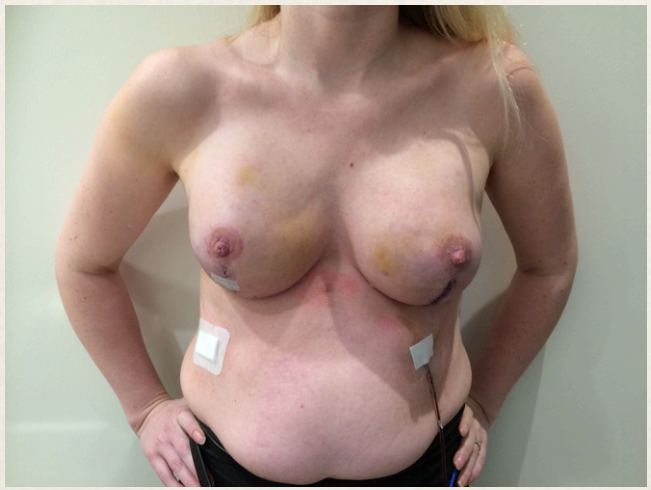
Treatment Options

- Neo-adjuvant chemotherapy
- Breast Conservation Surgery
- Unilateral mastectomy +/- reconstruction
- Bilateral mastectomy +/- reconstruction
- Bilateral salpingoophorectomy at time of breast surgery

The plan.....

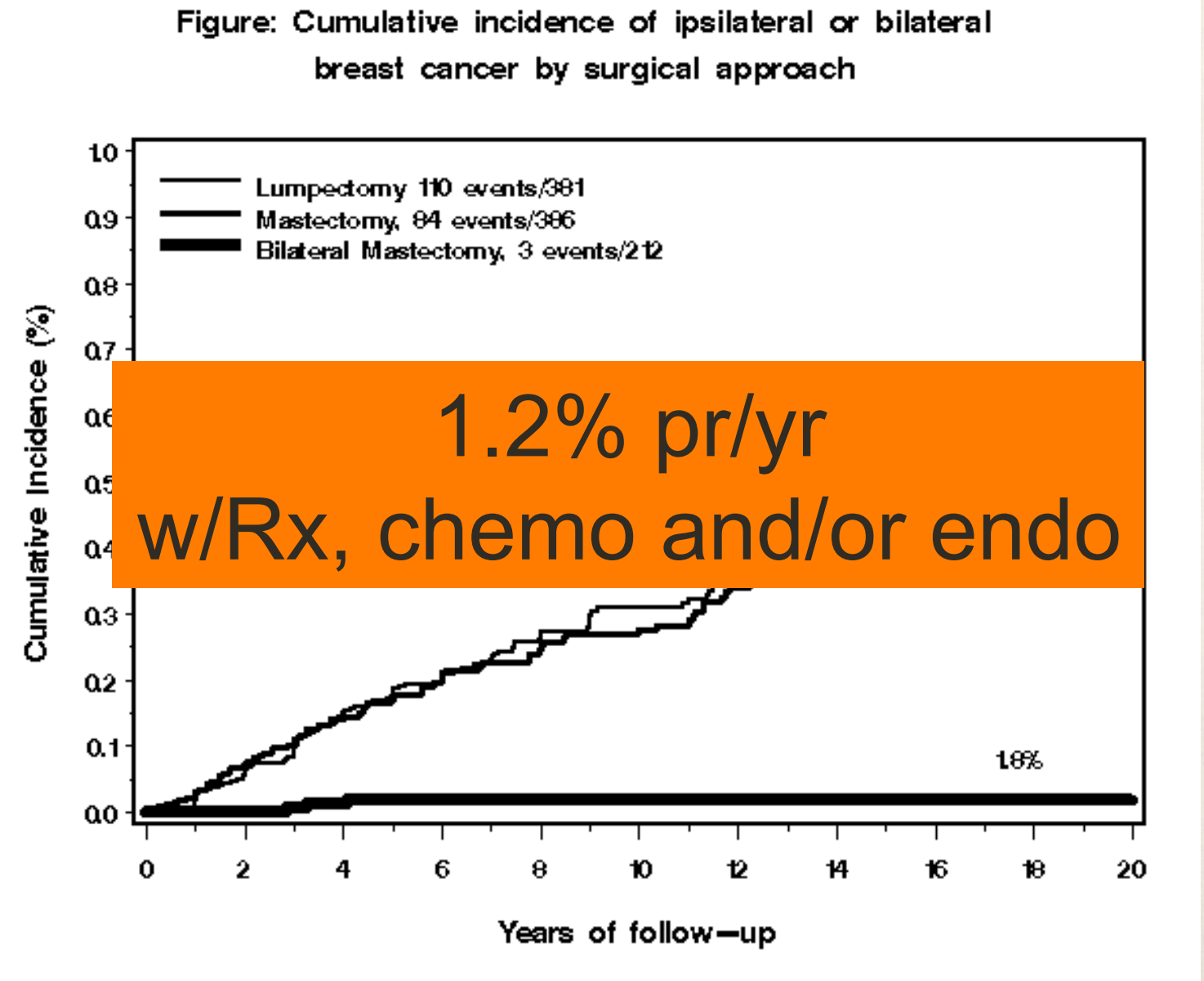






Wide local excision (therapeutic mammoplasty), SNB Left breast reduction → Adjuvant chemotherapy → Bilateral nipple sparing mastectomies with DTI reconstruction and BSO

Local Recurrence



1.2% pr/yr
w/Rx, chemo and/or endo

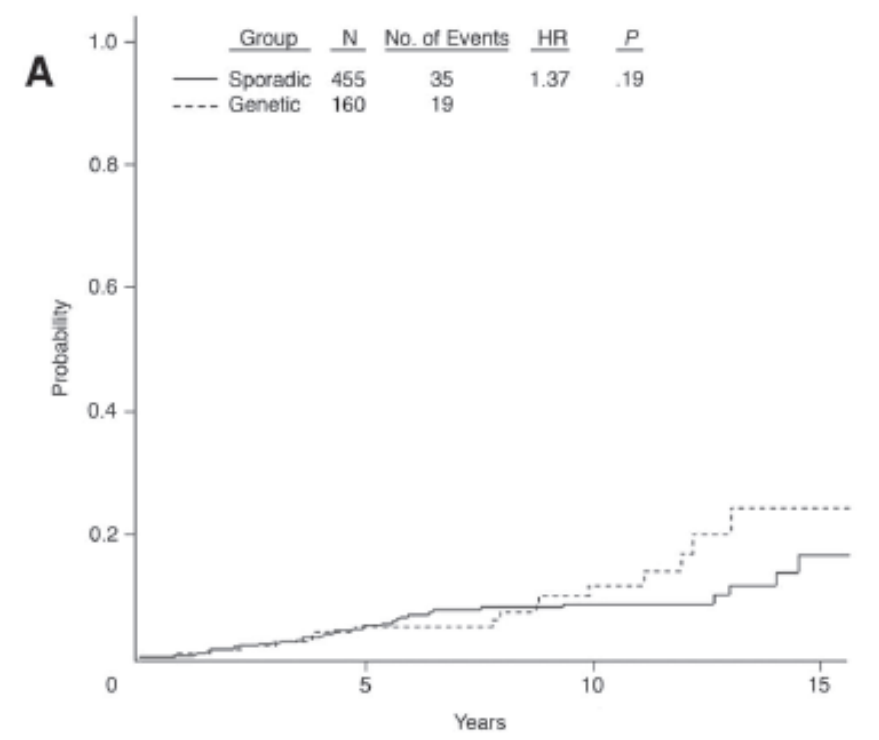
VOLUME 24 · NUMBER 16 · JUNE 1 2006

JOURNAL OF CLINICAL ONCOLOGY

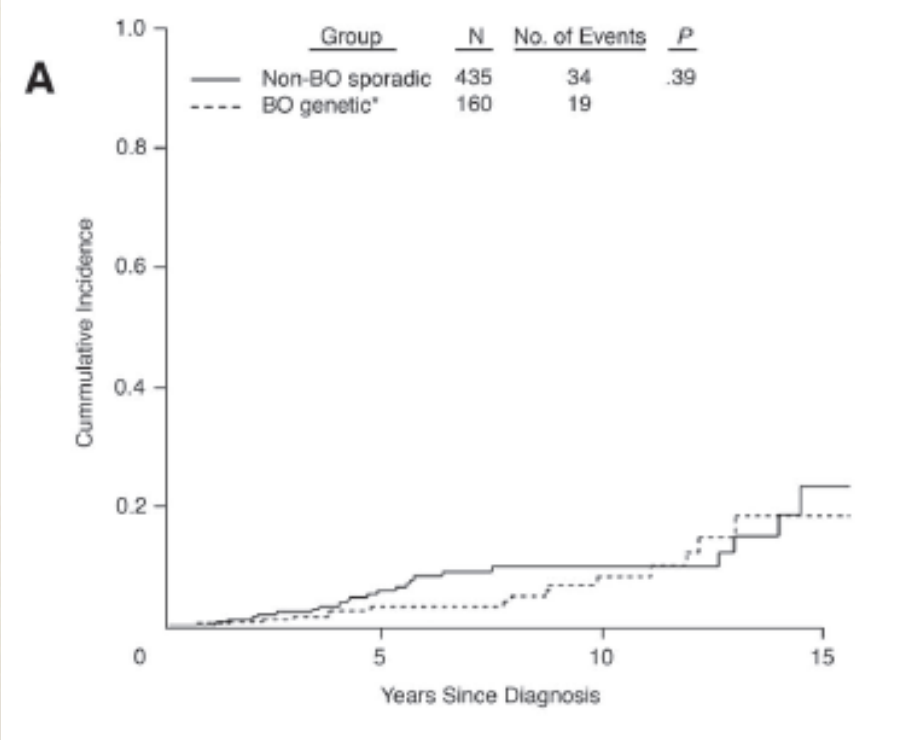
ORIGINAL REPORT

Ten-Year Multi-Institutional Results of Breast-Conserving Surgery and Radiotherapy in *BRCA1/2*-Associated Stage I/II Breast Cancer

Lori J. Pierce, Albert M. Levin, Timothy R. Rebbeck, Merav A. Ben-David, Eitan Friedman, Lawrence J. Solin, Eleanor E. Harris, David K. Gaffney, Bruce G. Haffty, Laura A. Dawson, Steven A. Narod, Ivo A. Olivotto, Andrea Eisen, Timothy J. Whelan, Olufunmilayo I. Olopade, Claudine Isaacs, Sofia D. Merajver, Julia S. Wong, Judy E. Garber, and Barbara L. Weber



Over-all IBTR BRCA vs. sporadic

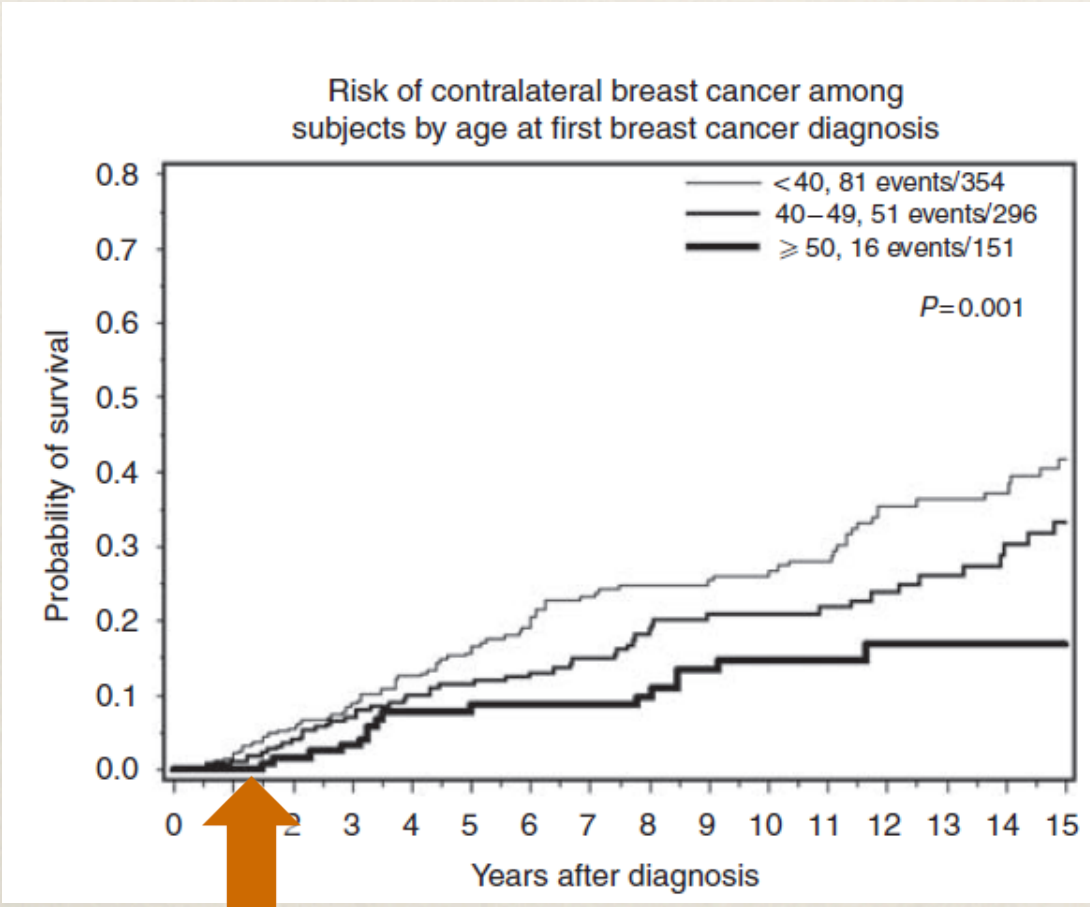


BRCA w/BSO vs. sporadic

Bilateral mastectomies

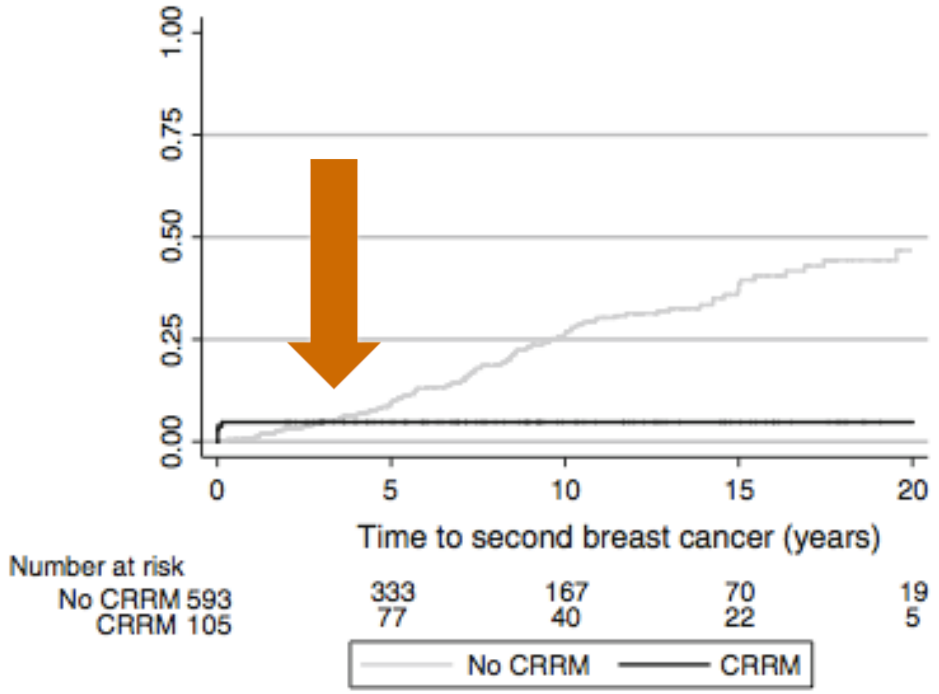
- Prevents local recurrence
  - Probably only of relevance after 10 years
  - Can be lowered with BSO
- Prevents contralateral breast cancer
  - Minimum risk up to 1.5-2 years after diagnosis
  - Risk is strongly related to age
- Prevents death
  - Probably no effect until after 10 years

Contralateral breast cancer



Metcalfe, K et al, BJC 2011

Rise of curves at 1.5 to 2.5 years



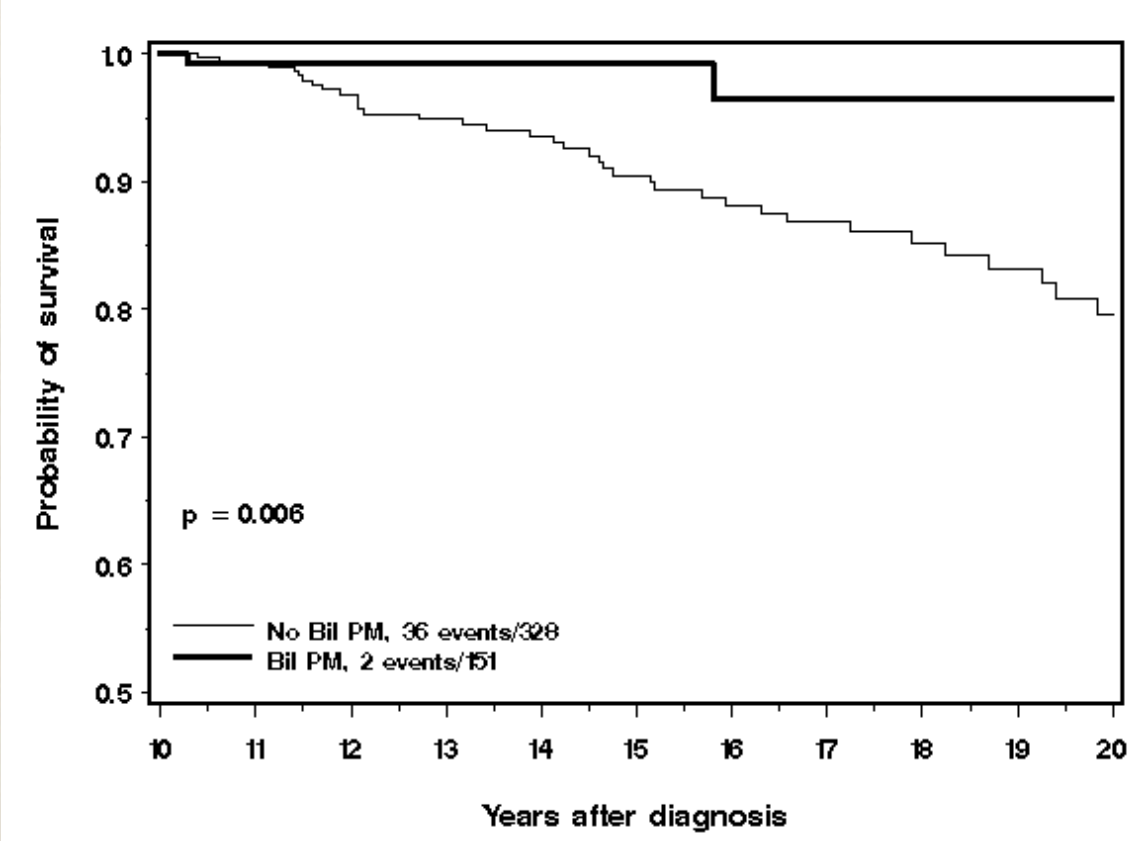
Evans DGR, et al, Breast Cancer Res Treat, 2013

Breast Cancer Mortality - BRCA

BRCA mutation	5years	10 years	15 years	20 years
BRCA 1	7%	15%	21%	30%
BRCA 2	4%	13%	20%	26%

Risk of death

Contralateral vs. no contralateral mastectomy



	N	Ipsi / contra	either	first surgery *	death
No Bil PM	328	12/37	44	174 Lum, 154 UM	36
Bil PM	151	1/2	3	43 Lum, 105 UM, 3 Bil M	2

* the 2nd surgery of the 151: for the 43, 30 had BPM, 13 had contra PM; for the 105 UM
for the 3 had Bil M, no further surgery.

Narod S, with kind permission

Breast cancer specific mortality

(676 patients with BRCA1 or 2 with stage 1 or 2 disease)

	Univariate RR (95% CI) P	Multivariate [a] RR (95%CI) P
Chemotherapy	0.97 (0.67-1.38) 0.84	0.72 (0.46-1.14) 0.16
Oophorectomy[b]	0.47 (0.29-0.76) 0.02	0.46 (0.27-0.79) 0.05
Ipsilateral Mastectomy (versus lumpectomy)	1.03 (0.54-1.08) 0.90	1.19 (0.67-1.26) 041
Contralateral Mastectomy[b]	0.60 (0.34-0.87) 0.03	0.59 (0.36-0.92) 0.07

[a] Adjusted for age at diagnosis, year of diagnosis, BRCA gene (BRCA1 or BRCA2), tumour size (cm), nodal status (positive/negative), ER status (+, -, missing), chemotherapy, tamoxifen, oophorectomy and contralateral mastectomy

[b] Time-dependent variable

Metcalfe K et al, JAMA Oncol. 2015;1(3):306-313

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