# Riskreducing mastectomy and familial breast cancer risk - who and when?

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Niklas Loman, medical oncologist SUS

# Who will benefit from a

Bilateral primary riskreducing mastectomy

Contralateral (and ipsilateral) riskreducing mastectomy after a previous breast cancer diagnosis

?

Simple rule of thumb:

# High risk – more benefit

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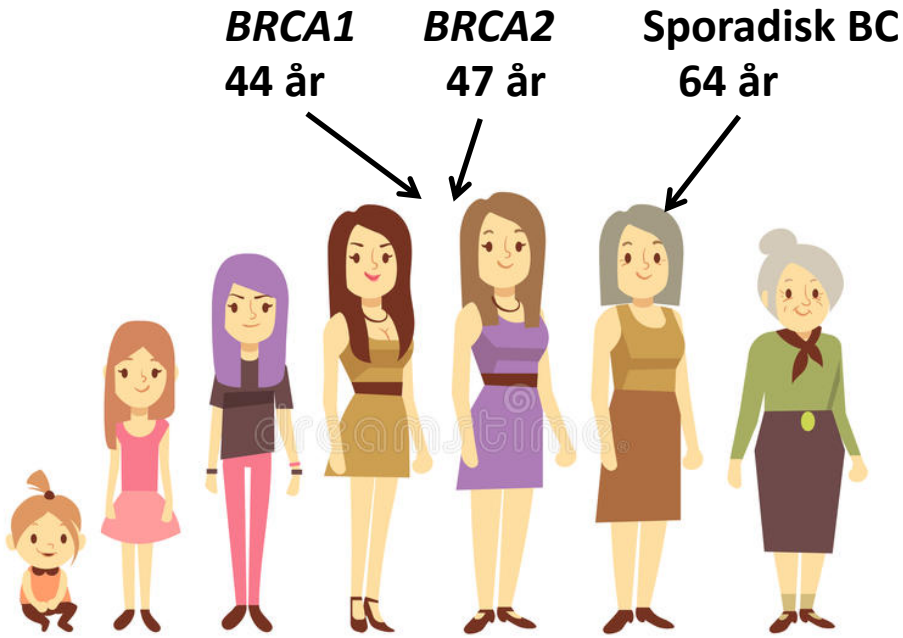
# High risk – more benefit

# Identify mutation carriers!

## *BRCA1 and BRCA2*

- **Identified in 1994 and 1995**
- **Not that rare** 0,2% of ♀ population ≈ 9800 women in Sweden
- **Early onset**
- **High risk breast cancer**[1]
  - BRCA1 72% (65-79%)
  - BRCA2 69% (61-77%)
- **High risk ovarian cancer**
  - BRCA1 40-60 %
  - BRCA2 10-20 %




[1]Kuchenbaecker 2017

Familial Cancer (2017) 16:187–193
DOI 10.1007/s10689-016-9953-x

ORIGINAL ARTICLE

# Efficacy versus effectiveness of clinical genetic testing criteria for BRCA1 and BRCA2 hereditary mutations in incident breast cancer

Martin P. Nilsson[1,2] · Christof Winter[1,3] · Ulf Kristoffersson[4,5] · Martin Rehn[6] · Christer Larsson[7] · Lao H. Saal[1,8] · Niklas Loman[1,2]

***Efficacy*** = the performance under ideal circumstances.

***Effectiveness*** = the performance under ”real world” circumstances.

Breast Cancer Research and Treatment (2018) 168:117–126
https://doi.org/10.1007/s10549-017-4584-y

CLINICAL TRIAL

# BRCAsearch: written pre-test information and *BRCA1/2* germline mutation testing in unselected patients with newly diagnosed breast cancer

Martin P. Nilsson[1,2] · Therese Törngren[1] · Karin Henriksson[3] · Ulf Kristoffersson[3,4] · Anders Kvist[1] · Barbro Silfverberg[3] · Åke Borg[1] · Niklas Loman[1,2]

BRCAsearch

Population testing in association with breast cancer diagnosis

Dr Martin Nilsson Ph D

# Invited/tested 542/818 = 67%

# Mutation carriers: N = 11; 2,0%
# + two previously known carriers: 2,4%

| Mutation (BIC) | Age at diagnosis (years) | St. Gallen subtype | TNM stage (AJCC 7th Edition) |
|---|---|---|---|
| **BRCA2 9808delCC, Stop 3195** | 70 | LumB HER2- | T1N0M0 |
| **BRCA2 8803delC, Stop 2862** | 49 | LumB HER2- | T1N1miM0 |
| **BRCA1 1806C>T, Q563X** | 46 | Basal | cT2pN0M0; ypTisN0** |
| **BRCA2 6174delT, Stop 2003** | 68 | LumB HER2- | T1N0M0 |
| | | | |
| **BRCA2 6495delGCAinsC, Stop 2090** | 63* | LumB HER2- | cT2N1M0; ypT0N0** |
| **BRCA2 8953+1G, IVS22+1G>T** | 65 | LumB HER2- | T1N0M0 |
| **BRCA2 4486delG, Stop 1447** | 47* | LumB HER2- | T1N2M0 |
| **BRCA2 4486delG, Stop 1447** | 72 | LumB HER2- | T1N0M0 |
| **BRCA1 1806C>T, Q563X** | 57* | LumB HER2- | T1N0M0 |
| **BRCA2 4486delG, Stop 1447** | 68* | LumB HER2- | cT2N1M0; ypT0N0** |
| **BRCA2 5447delT, Stop 1740** | 40 | LumB HER2+ | T1N0M0 |

**Previous diagnosis of breast cancer in the contralateral breast; age refers to age at diagnosis of the second primary breast cancer

**Neoadjuvant chemotherapy

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CLINICAL TRIAL

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# Predictors of accepting testing:

Age over 80: (OR = 0,10 P=0,002)

Psyciatric disease: (OR = 0,46 P = 0,006)

At least three years at University (OR = 2,03 P = 0,003))

Breast-/ovarian cancer in first or second degree relatives (OR = 1,66 P = 0,02)

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CLINICAL TRIAL

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# Simplified testing procedure in South Sweden region since October 2017

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But we need på find more carriers!

# Increase testing criteria!

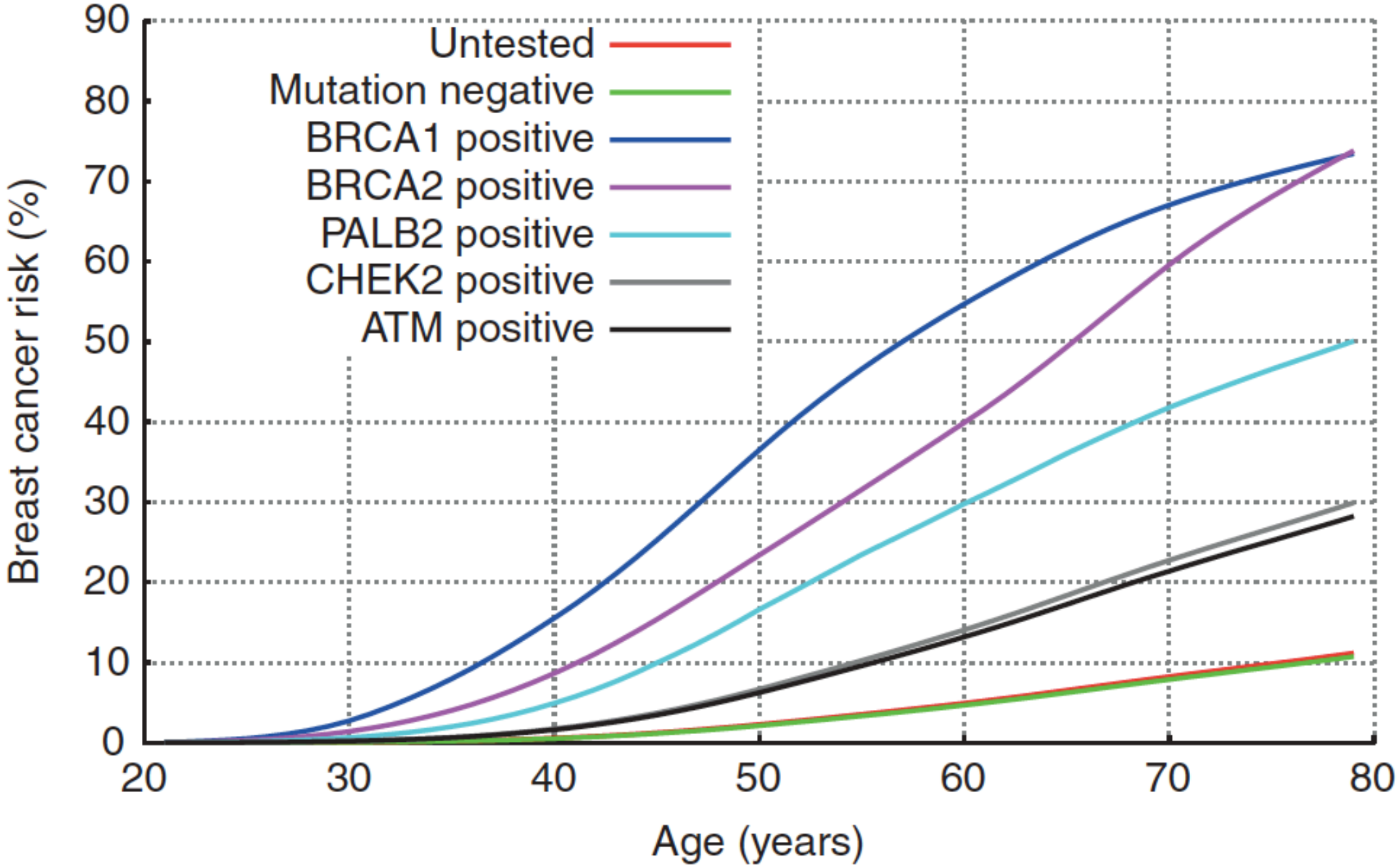
**Sammanfattande rekommendationer för cancergenetisk utredning inklusive molekylärgenetisk testning**

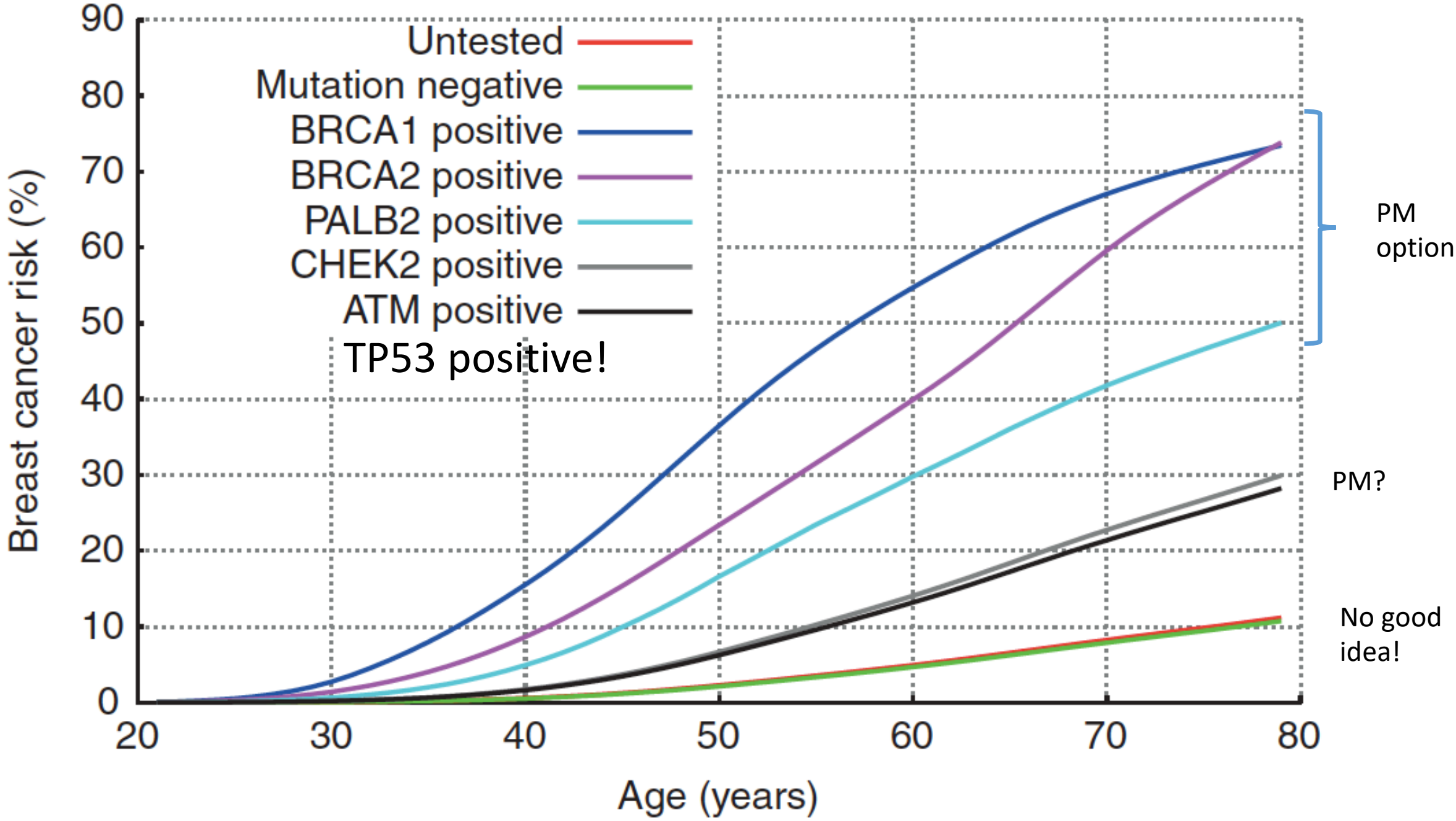
- Bröstcancer ≤ 40 års ålder.
- Bröstcancer ≤ 50 år, om det i samma släktgren finns minst ett ytterligare fall av bröstcancer hos förstagradssläktingar eller andragradssläktingar. Bilateral bröstcancer räknas som två fall. Det andra fallet kan också vara ovarialcancer, tidig prostatacancer (före 65 års ålder), eller pancreascancer.
- Bröstcancer ≤ 60 år, om det i samma släktgren finns minst två ytterligare fall av bröstcancer hos förstagradssläktingar eller andragradssläktingar. Bilateral bröstcancer räknas som två fall. De andra fallen kan också vara ovarialcancer, tidig prostatacancer (före 65 års ålder), eller pancreascancer.
- Trippelnegativ bröstcancer ≤ 60 års ålder.
- Manlig bröstcancer oavsett ålder.
- Ovarialcancer inklusive tubarcancer och primär peritoneal carcinomatos (icke-mucinös, icke-borderline) oavsett ålder.
- Kriterier uppfyllda för annat ärftligt syndrom där bröst-/ovarialcancer ingår, se avsnitt 10.3.3.

# Test for more genes!

SWEA-study – national cohort of panel testing in families with suspected hereditary breast cancer (April 2012 – April 2017, 3988 families tested for 64 genes

| Gen | Antal patogena / sannolikt patogena (ej VUS) | Totalt | Frekvens | Kommentar |
|---|---|---|---|---|
| *BRCA1* | 237 | 3988 | 5,94% | |
| *BRCA2* | 120 | 3988 | 3,01% | |
| *TP53* | 30 | 3988 | 0,75% | 24 heterozygota, 6 mosaiska |
| *PTEN* | 0 | 3988 | 0,00% | |
| *CDH1* | 1 | 3988 | 0,03% | |
| *STK11* | 0 | 3988 | 0,00% | |
| *PALB2* | 31 | 3988 | 0,78% | |
| *RAD51C* | 22 | 3988 | 0,55% | |
| *RAD51D* | 5 | 3988 | 0,13% | |
| *BRIP1* | 17 | 3988 | 0,43% | |
| *CHEK2* trunkerande | 140 | 3988 | 3,51% | 118 st 1100delC, 22 andra |
| *ATM* trunkerande | 60 | 3988 | 1,50% | |
| *NBN* trunkerande | 8 | 3988 | 0,20% | |
| *MSH2, MLH1, MSH6, PMS2, EPCAM* | - | - | - | ej i SWEA |
| *NF1* | - | - | - | ej i SWEA |


Untested
Mutation negative
BRCA1 positive
BRCA2 positive
PALB2 positive
CHEK2 positive
ATM positive
Breast cancer risk (%)
0
10
20
30
40
50
60
70
80
90
20
30
40
50
60
70
80
Age (years)


Breast cancer risk (%)
90
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0
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30
40
50
60
70
80
Age (years)
Untested
Mutation negative
BRCA1 positive
BRCA2 positive
PALB2 positive
CHEK2 positive
ATM positive
TP53 positive!
PM option
PM?
No good idea!

# VUS – variant of unknown significance

primary risk reducing mastectomi

The American Journal of Surgery (2016) 212, 660-669

The American Journal of Surgery®

Association of Women Surgeons

# Risk reduction and survival benefit of prophylactic surgery in *BRCA* mutation carriers, a systematic review

Kandice K. Ludwig, M.D.[a], Joan Neuner, M.D., M.S.[b], Annabelle Butler, M.D.[c], Jennifer L. Geurts, M.S.[d], Amanda L. Kong, M.D., M.S.[c,*]

[a]*Department of Surgery, Indiana University School of Medicine, Carmel, IN, USA;* [b]*Division of General*

Systematic overview 2016
ten studies (BRCA1 och BRCA2)

- 90 – 95 % risk reduction in terms of breast events
- No *proven* survival benefit by risk reducing ME

**Reduced incidence of breast and ovarian cancer has resulted in an improved survival in carriers**

HR for death in the order of 0,30

contralateral risk reducing mastectomy

Cochrane Library

Cochrane Database of Systematic Reviews

2004, 2006, 2010, 2018

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

Carbine NE, Lostumbo L, Wallace J, Ko H

Observationella studier 9900 kvinnor som genomgick CRRM för unilateral bröstcancer

- CRRM gruppen var yngre, gifta, högre utbildade
- kohortmix - familjär risk/BRCA-mut
- BRCA-mut kvinnor får bättre OS av CRRM
- CRRM tenderar ge bättre OS för:
  - → ER neg > ER pos
  - → kvinnor <60 år

**Insufficient evidence that CRRM improves survival after a unilateral breast cancer!**

# Contralateral breart cancer risk in BRCA1 and BRCA2

| 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) |

**Early onset of first breast cancer predicts increased risk!**

JAMA | Original Investigation

Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

Karoline B. Kuchenbaecker, PhD; John L. Hopper, PhD; Daniel R. Barnes, PhD; Kelly-Anne Phillips, MD; Thea M. Mooij, MSc; Marie-José Roos-Blom, MSc; Sarah Jervis, PhD; Flora E. van Leeuwen, PhD; Roger L. Milne, PhD; Nadine Andrieu, PhD; David E. Goldgar, PhD; Mary Beth Terry, PhD; Matti A. Rookus, PhD; Douglas F. Easton, PhD; Antonis C. Antoniou, PhD; and the *BRCA1* and *BRCA2* Cohort Consortium

# Breast cancer specific survival and contralateral mastectomy in BRCA mutation carriers after unilateral breast cancer:

Metcalf et al 2014

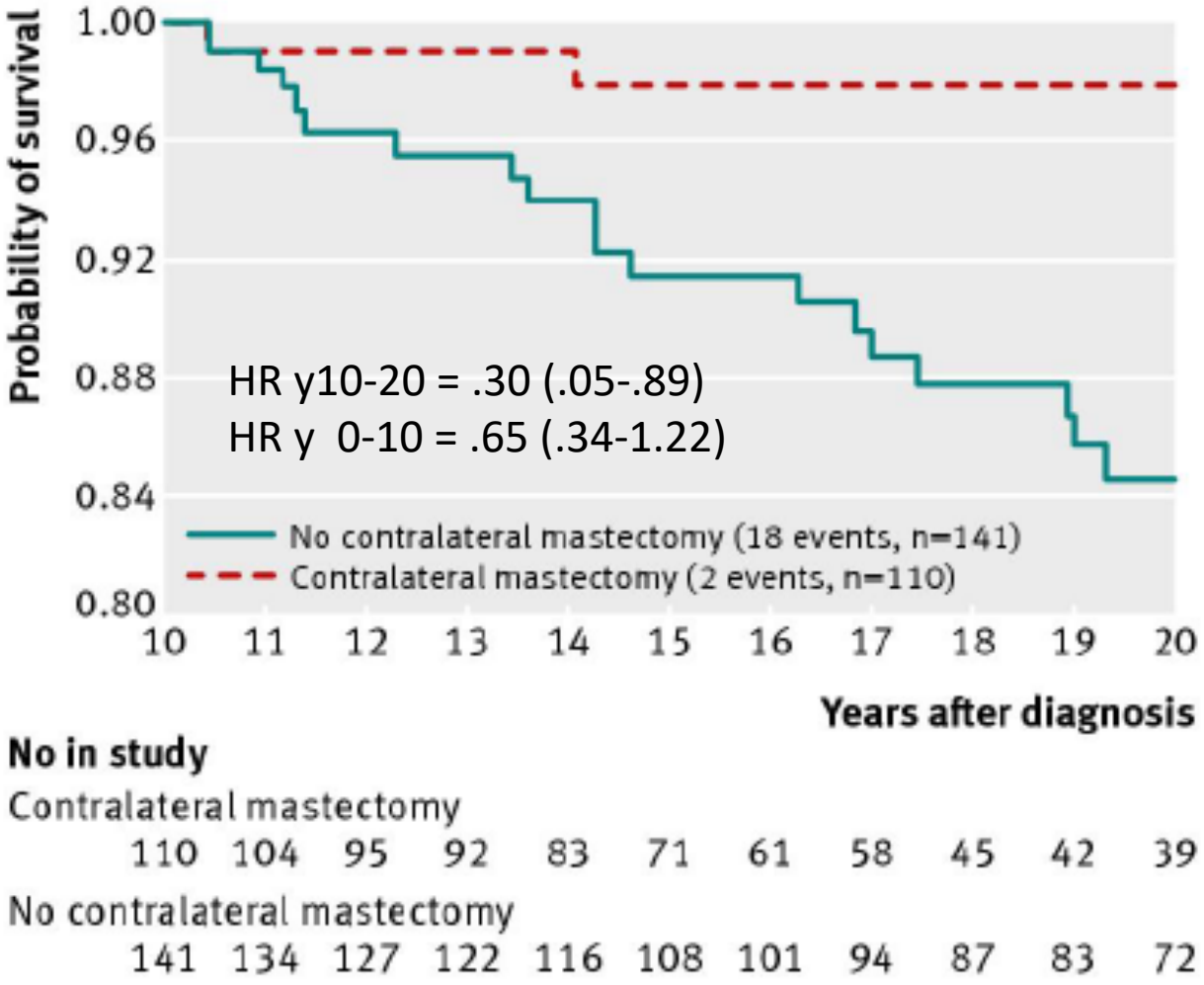

- Retrospectiv cohort N=390

  BRCA bärare, stage 1-2

- 181 contralateral ME

- FU median 13 y (0,1-20)

# Survival after 10 years




Supports a beneficial effect in terms of survival after contalateral ME in BRCA-carriers – in the long run!

# Two other studies show similar results

IJC
International Journal of Cancer

## Improved overall survival after contralateral risk-reducing mastectomy in brca1/2 mutation carriers with a history of unilateral breast cancer: A prospective analysis

Bernadette A.M. Heemskerk-Gerritsen[1], Matti A. Rookus[2], Cora M. Aalfs[3], Margreet G.E.M. Ausems[4], Johanna M. Collée[5], Liesbeth Jansen[6], C. Marleen Kets[7], Kristien B.M.I. Keymeulen[8], Linetta B. Koppert[9], Hanne E.J. Meijers-Heijboer[10], Thea M. Mooij[2], Rob A.E.M. Tollenaar[11], Hans F.A. Vasen[12], HEBON[13], Maartje J. Hooning[1†] and Caroline Seynaeve[1†]

Breast Cancer Res Treat (2013) 140:135–142
DOI 10.1007/s10549-013-2583-1

EPIDEMIOLOGY

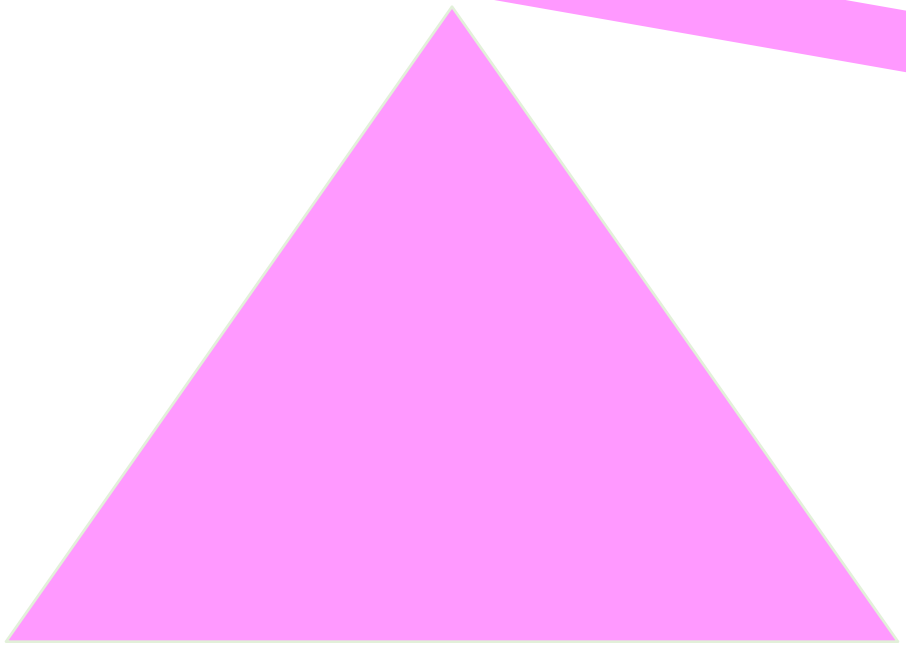
## Contralateral mastectomy improves survival in women with *BRCA1/2*-associated breast cancer

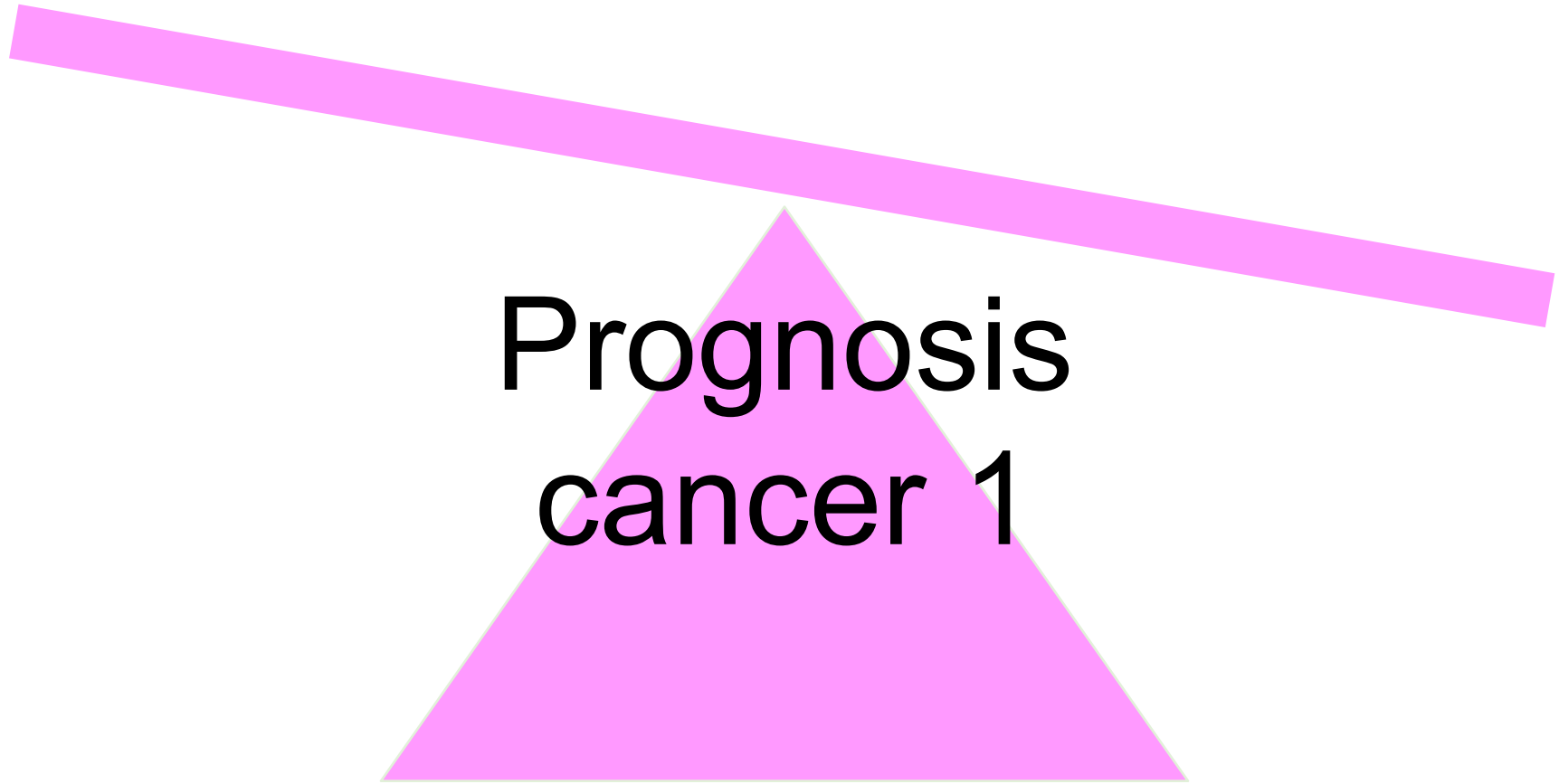
D. Gareth R. Evans · Sarah L. Ingham · Andrew Baildam · Gary L. Ross · Fiona Lalloo · Iain Buchan · Anthony Howell

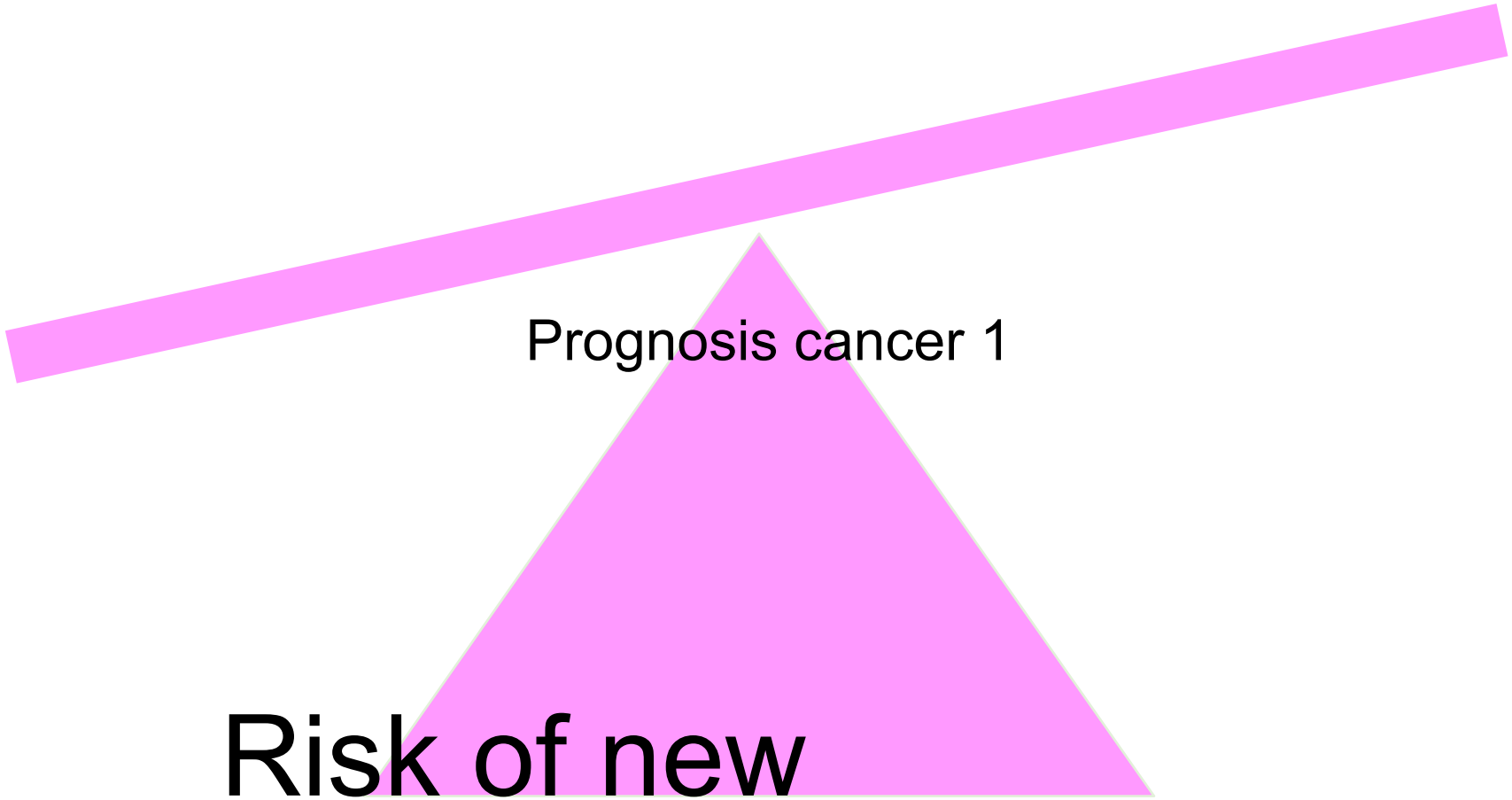
# The others then?

- PALB2: no data but probably resaonable to treat like BRCA1 and BRCA2
- TP53 requires special attention – acknowledge high risk of other malignancies – but resonable to offer risk reducing surgeries
- Non-carriers with a positive family history?

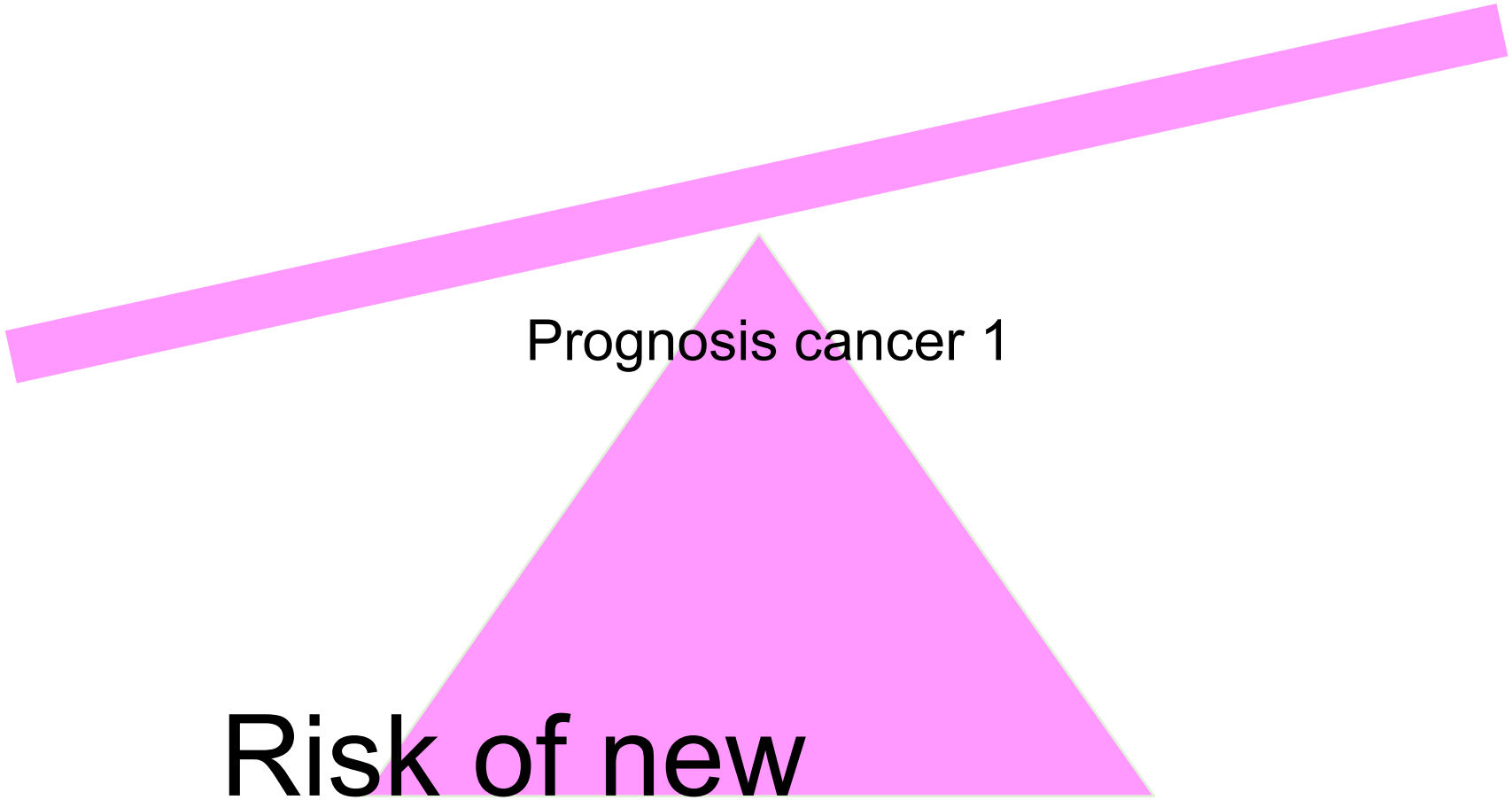
# What should affect a decision on contralateral mastectomy?




Prognosis
cancer 1

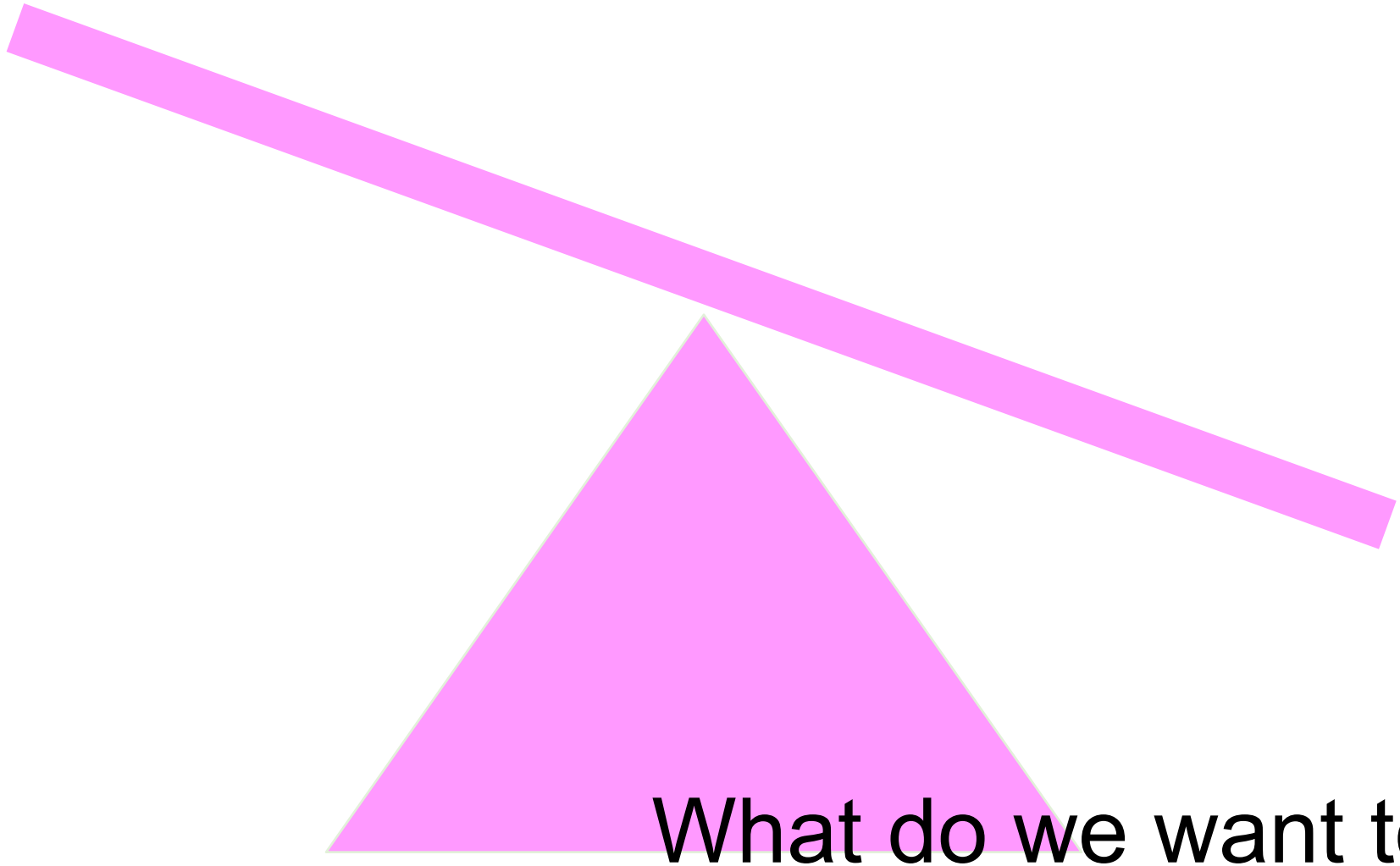



Risk of new primary breast cancer(!)




# Risk of new primary breast cancer(!)

Mutation – BRCA1/2
Family history ?
Treatment cancer 1?



What do we want to acheive?


Prognos 1
Prognos 2
Risk att insjukna
Vad vill man uppnå?

# Manchester model

1) Medical history, expectations?
2) Calculate the risk
3) ”Cooling-off period”
4) MDT
5) Decision - consent

# Estimation of contralaterl breast cancer according to Manchester (Basu et al 2015)

- Assume 0,5 % risk per year for a contralateral bc
- Count on 80 yeras life expectancy
  - Basic risk: (80y – curren age) * 0,5 %
    - If ER+ and ET: multiply by 0,5
    - If mutation carrier: multiply by 4
    - If  Family history: multiply by 2
    - If ooforectomi before 40: multiply by 0,5

Basu *et al. World Journal of Surgical Oncology* (2015) 13:237
DOI 10.1186/s12957-015-0638-y

WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH Open Access

The Manchester guidelines for contralateral risk-reducing mastectomy

Narendra Nath Basu[1,4*], G L Ross[2], D G Evans[1,3] and L Barr[1]

# Två exemples

- 50 year woman with a ER+ breast cancer, no FH, treated with tamoxifen
  - 7,5%

- 45 year ER-negative breast cancer and a mother with breast cancer – no known mutation
  - 35 %

# BOADICEA

Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm

- Calculates
  - risk to carry a mutation in one of several genes (BRCA, PALB2, ATM and CHEK2)
  - Age specific risk of breast and ovarian cancer

- Developed 2002-2008 baserad on UK population based material (Antoniou et al),
- Validated in Sverige (Ståhlbom et al 2012)

# BOADICEA web application 4.0

search | a-z | contact

UNIVERSITY OF CAMBRIDGE

Centre for Cancer Genetic Epidemiology

BOADICEA — Computed Results

Computed results for the Target: Patient(1)

| Genetic Status | Mutation Carrier Probabilities (Percent) |
|---|---|
| BRCA1 | 8.8 |
| BRCA2 | 1.3 |
| PALB2 | 0.9 |
| ATM | 1.0 |
| CHEK2 | 0.4 |
| No Mutation | 87.6 |

| Model Parameters | |
|---|---|
| Target Family Member | Patient(1) |
| Mutation Frequencies: UK<br>BRCA1: 6.394d-4<br>BRCA2: 0.00102<br>PALB2: 0.000575<br>ATM: 0.001921<br>CHEK2: 0.002614 | Mutation Search Sensitivities: Default<br>BRCA1: 0.7<br>BRCA2: 0.8<br>PALB2: 0.9<br>ATM: 0.9<br>CHEK2: 1.0 |
| Cancer Incidence Rates | UK |

| Age | Contralateral Breast Cancer Risks (Percent) | Ovarian Cancer Risks (Percent) |
|---|---|---|
| 31 | 0.3 | 0.0 |
| 32 | 0.6 | 0.0 |
| 33 | 0.9 | 0.0 |
| 34 | 1.2 | 0.1 |
| 35 | 1.6 | 0.1 |
| 40 | 3.9 | 0.3 |
| 45 | 7.0 | 0.7 |
| 50 | 10.6 | 1.2 |
| 55 | 14.0 | 1.7 |
| 60 | 17.1 | 2.4 |
| 65 | 20.0 | 3.1 |
| 70 | 22.5 | 3.9 |
| 75 | 24.4 | 4.7 |
| 80 | 25.7 | 5.5 |

Logout | Reset | Go Back | Graph Breast Cancer Risks | Graph Ovarian Cancer Risks | Reformat | Generate Report


| Genetic Status | Mutation Carrier Probabilities (Percent) |
|---|---|
| BRCA1 | 8.8 |
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| No Mutation | 87.6 |


**Contralateral Breast Cancer Risks**

Age 80 26%

**Ovarian Cancer Risks**

Age 80 5,5%

# Contralateral riskreducerande mastektomi – thus:

- BRCA-carriers: Strong evidence for morbidity reduction, Moderate evidence for survival benefit.
    - Treat the cancer first!
    - Estimaate the  prognosis!
    - Age matters
    - Previous ovarian cancer?
- Unclear evidence, but reasonable in case of mutation in other high penetrant genes: TP53, PALB2
- Unclear in case of intermediatly penetrant genes (CHEK2, ATM och NBN) – Family history assessment!
- Most others very limited benefit!
    - Perhaps: early onset strong family history including bilateral disease in first degree relative

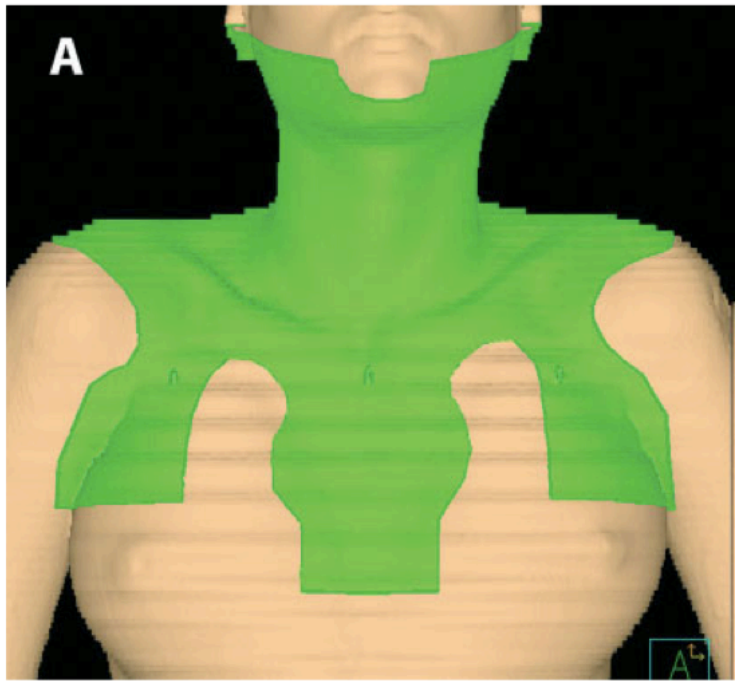
# Primary risk reducing mastectomi:

- BRCA-mutation carriers – yes! If she thinks it is a goos idea!
- Reasonable in other hogh penetrant genes TP53 (!), PALB2(?)
- Moderately penetrant genes, lack of evidence, CHEK2, ATM, NBN
- No indication in epidemiologically defined risk

# Riskreducerande mastektomi - indikationer

## Tidigare genomgången strålbehandling mot bröstvävnad

- Pat med bröstcancer som fått mantelstrålbehandling som ung




| Författare | Land | År | Studieform | Antal | Risk |
|---|---|---|---|---|---|
| Dores | USA | 2010 | Register<br>SEER | 2645<br>RT<35 åå | HR=6,13 (5,23-7,13)<br>BRCA1/2 HR=5-8 |

Focus on high risk – test for high penetrant genes!

**Talk to your clinical geneticist!**