The Breast Surgeon and the High-Risk Individual

Current Evidence for Risk-Management and Breast Cancer Treatment Strategies

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Jean Hailes CPD Day - Sat 22nd March 2025

Jane O'Brien
Specialist Breast Surgeon

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Waiting for the other shoe to drop...

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"To await a seemingly inevitable event, especially one that is not desirable"

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For the vast majority of women choosing Bilateral Risk-Reduction Mastectomy (BRRM), their choice is not predominantly driven by an intention to gain a survival benefit.

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In clinical practice, BRCA carriers opting for BRRM want to **AVOID:**

- The lifelong anxiety/distress related to intensive surveillance with a significant risk of false-positives, in the knowledge that 60 to 80% of them will still be confronted with a breast cancer diagnosis at some point.

- A high risk of having to undergo (neo) adjuvant chemotherapy, axillary surgery, radiotherapy, and/or endocrine treatment, with all the possible implications and long-term side effects.

- A 60 to 80% risk of switching from breast screening to breast cancer relapse surveillance for the rest of their life.

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Questions

- What is the **evidence** for risk-reducing surgery vs non-surgical risk management for high-risk individuals?

- What is the **evidence** for "more" or "less" surgery in the treatment of hereditary breast cancer?

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Answers

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- Most of the currently offered risk-management interventions are **"effective"**, within the limitations of what each can be reasonably expected to achieve

- Measure of intervention efficacy depends on the aim / goal of intervention

- Perception of **Risk / Benefit Ratio** associated with each intervention will differ, depending on the baseline level of risk, and the individual's tolerance of the side effect profile /complication rate vs their desired endpoint

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Defining / Categorising Breast Cancer Risk

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Risk categories	Cancer Australia[4]	eviQ[15,16] (based on NICE)[17]
Average risk	< 1.5 times population risk	11% LTR
Moderate risk	1.5 to 3 times population risk	≥ 17 but < 30% LTR
High risk	> 3 times population risk	≥ 30% LTR

Average / Moderate / High Risk Categories

- **Cancer Australia:** ratio of the estimated remaining lifetime risk to the residual lifetime population risk for a woman of the same age. **<1.5 / 1.5-3 / >3**
- **eviQ / NICE:** Lifetime risk from age 20 **<17% / 17-30 / >30**

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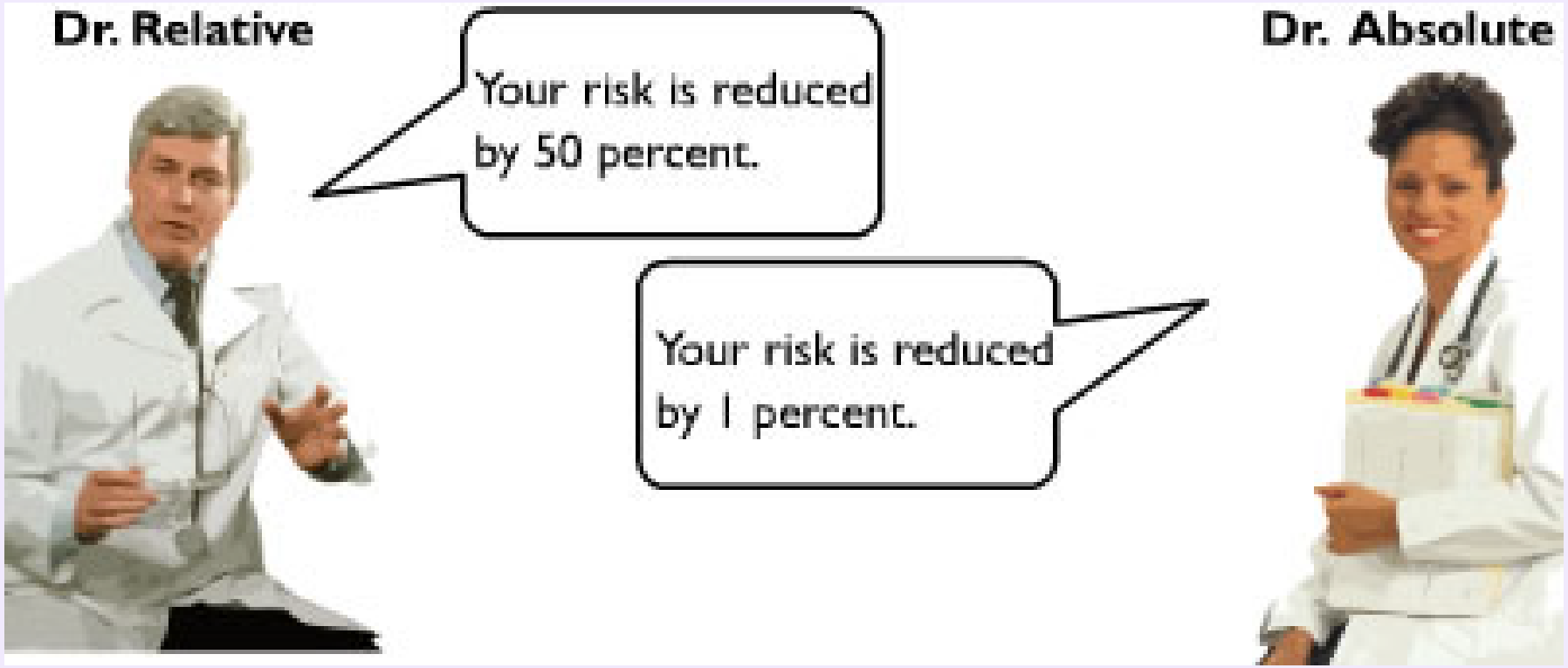
Defining "Risk-Reduction" to Patients



Framing is Important

- Framing risk information in positive terms (eg chance of survival) is more likely to persuade patients to accept risky options than information presented in negative terms (eg chance of death)
- Framing the benefit of a screening test in terms of what the patient might lose by not having it, has been shown to be more persuasive than framing involving potential gains.

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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

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Statistical innumeracy is very common

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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Table 1. Absolute risk reduction, relative risk reduction and number needed to vaccinate for COVID-19 vaccines. Data from phase 3 studies.

	Reference	*ARR (%)*	*RRR (%)*	*NNV*
BNT162b2 (Pfizer-BioNtech)	[3]	0.84	95.0	119
mRNA1273 (Moderna-NIH)	[4]	1.24	94.1	81
ChAdOx1nCoV19 (Astra Zeneca – Oxford)	[5]	1.11	72.8	90
Ad26CoV2S (Johnson & Johnson)	[6]	1.19	66.9	84
GamCovidVac (Gamaleya)	[7]	0.93	91.0	86
NVX-CoV2373 (Novavax)	[8]	1.23	89.7	82
CORONAVAC (Sinovac)	[9]	0.76	83.5	131
WIBP-CorV (Wuhan – Sinopharm)	[10]	0.54	72.8	185
BBIBP-CorV (Beijing – Sinopharm)	[10]	0.58	78.1	172

ARR = Absolute Risk Reduction; NNV = Number Needed to Vaccinate; RRR = Relative Risk Reduction.

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Relative Risk Reduction (RRR)
- **The ratio of attack rates with and without a vaccine**

95%

Absolute Risk Reduction (ARR) - 0.85%
- **The difference between attack rates with and without the vaccine**

0.84%

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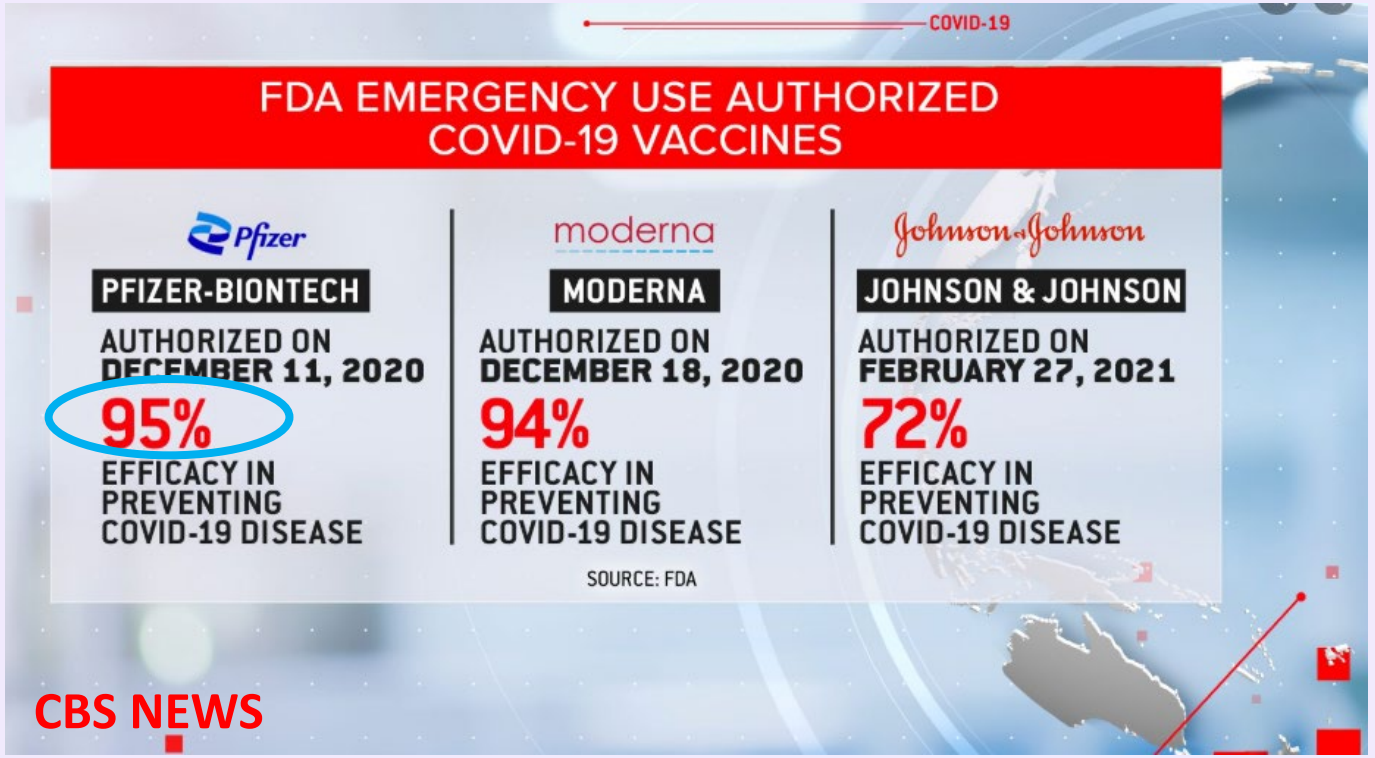

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- By reporting only RRR, the public was encouraged to believe that a vaccine with reported 95% efficacy means that 95% of vaccinated people will be protected, which is incorrect.
- The relative risk does not provide ANY information about the absolute risk of the event occurring, but rather the higher or lower likelihood of the event in the exposure versus the non-exposure group.

Relative risk reduction: Misinformative measure in clinical trials and COVID-19 vaccine efficacy

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Assume a given intervention reduces the risk of developing breast cancer by 95%

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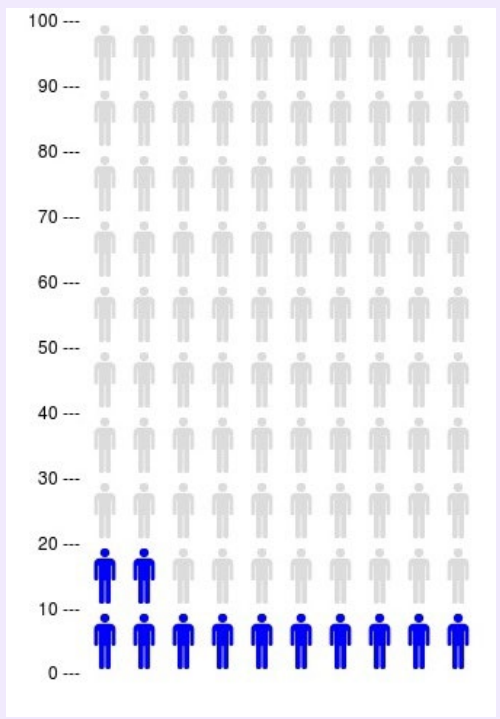
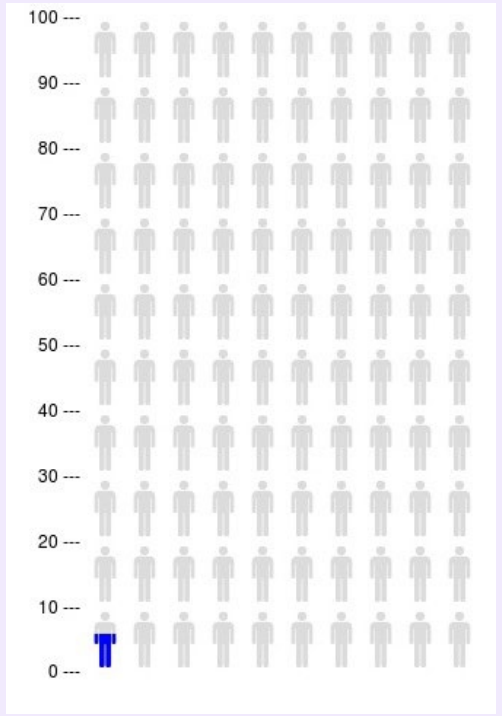
Average Risk Individual

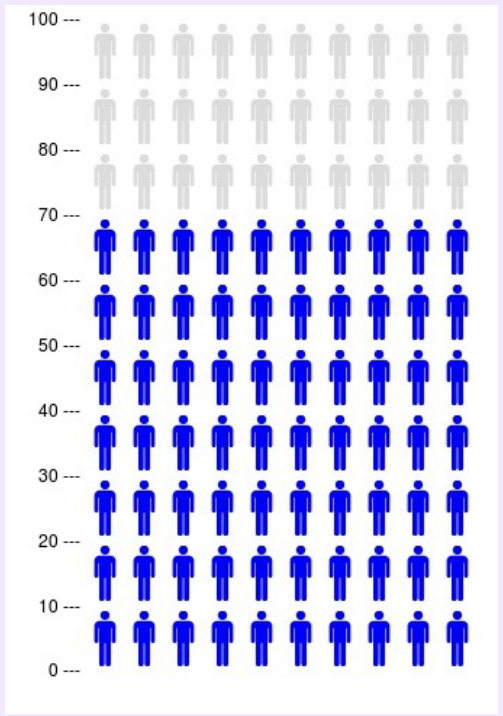


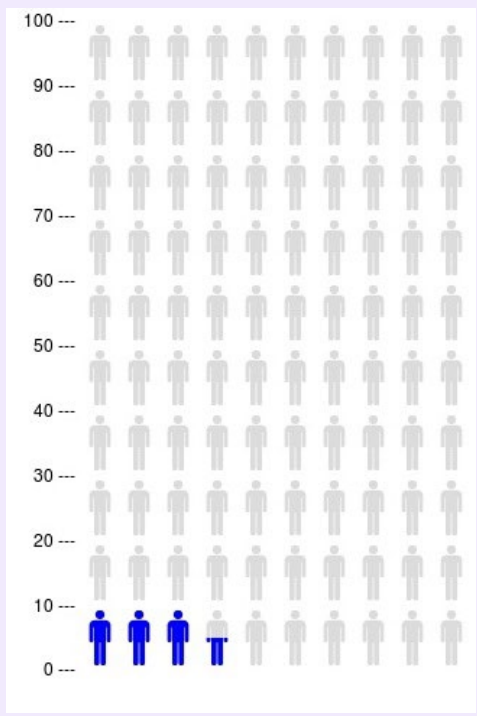


12/100 → 0.6/100

11.4 % absolute risk reduction

BRCA Carrier





70/100 → 3.5/100

67.5% absolute risk reduction

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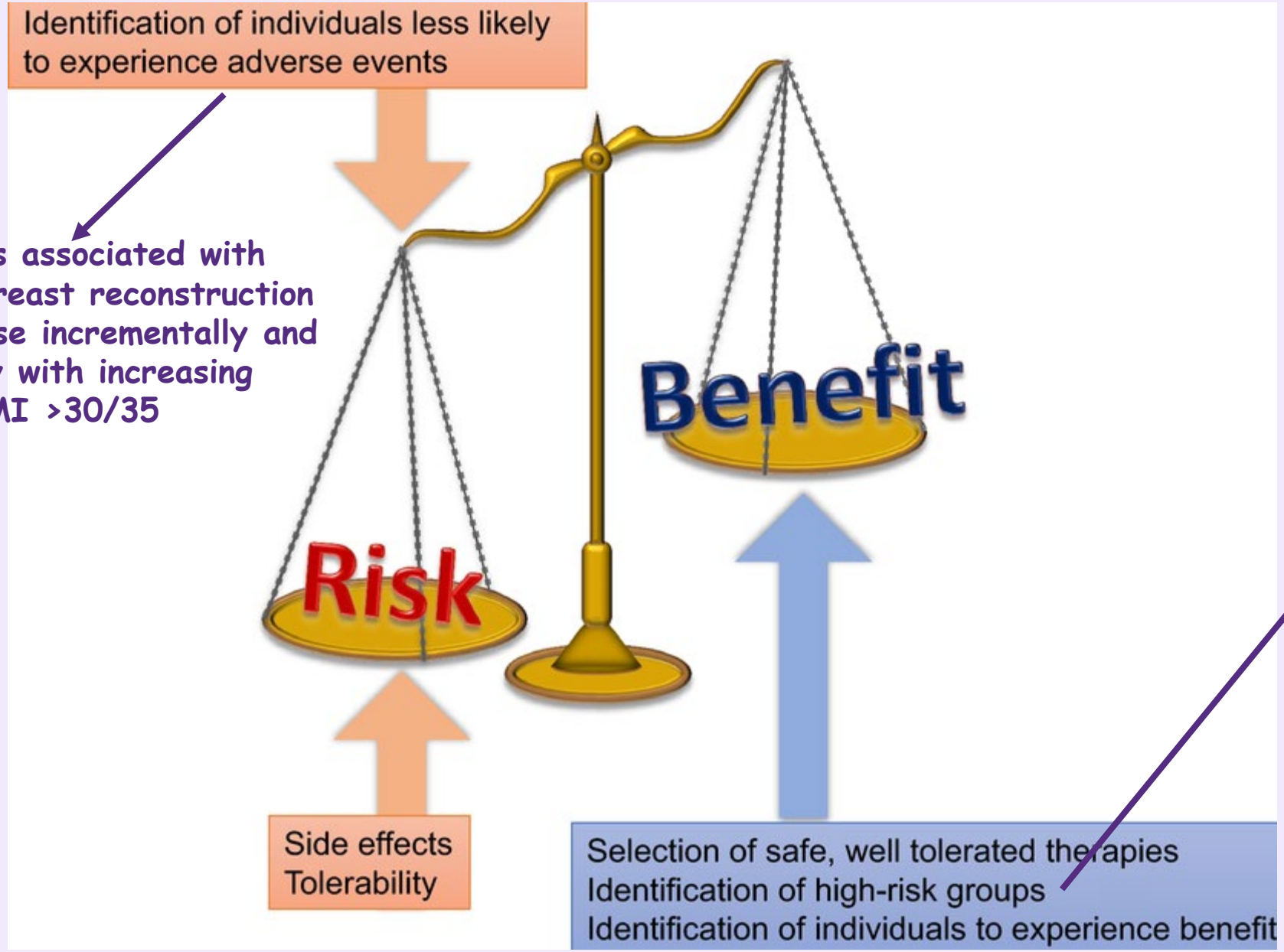
Complications associated with immediate breast reconstruction (IBR) increase incrementally and progressively with increasing BMI, esp BMI >30/35



Accurate risk-assessment vital

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Risk / Benefit Ratios Change over time, and with Circumstances

Perception of both risk AND benefit may differ between patient and doctor

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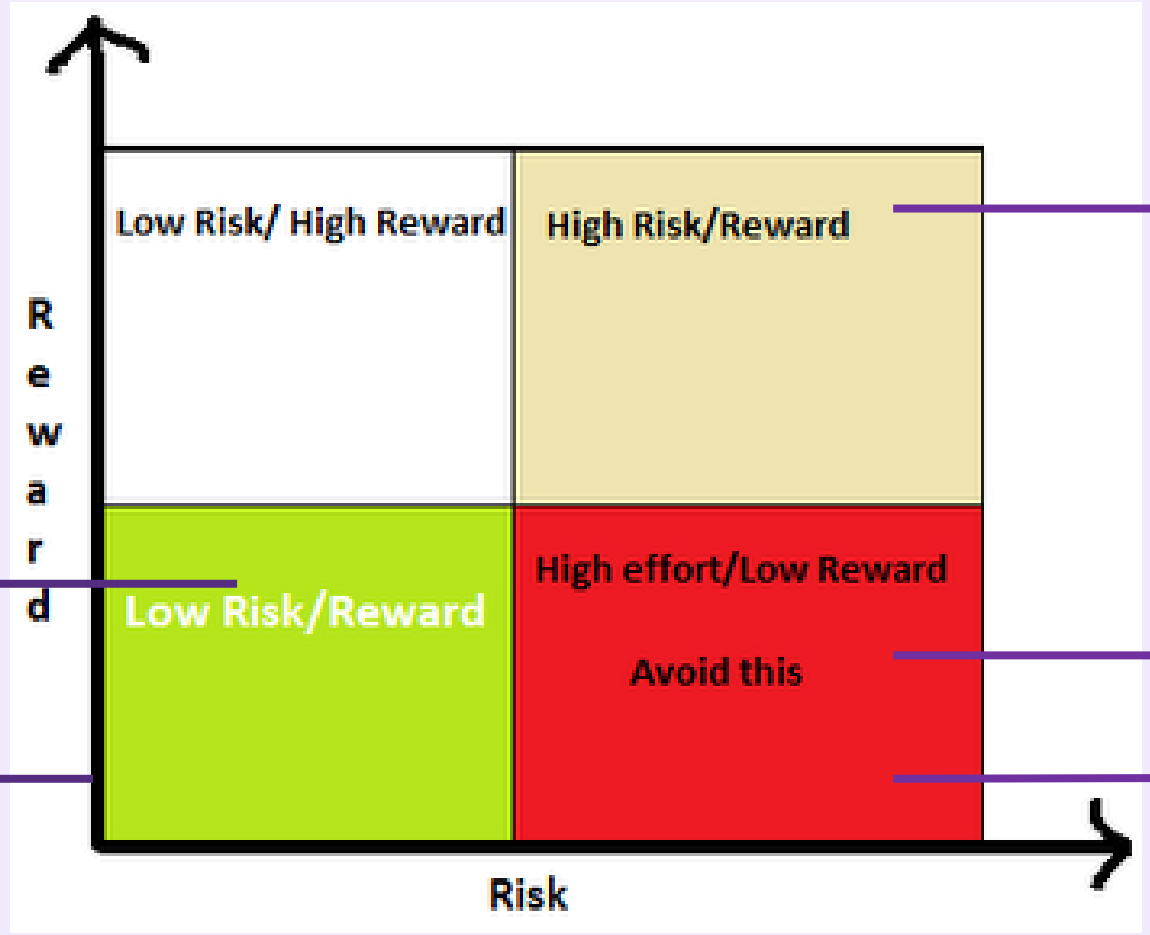

Unaffected individual with confirmed BRCA mutation at high increase breast cancer risk considering bilateral risk-reducing mastectomy (BRRM)

Risk-Reducing Medications in individual at mod increased risk

Affected individual with confirmed BRCA mutation and Stage 1V BC requesting bilateral mastectomy

Lifestyle modification

Unaffected individual at only sl increase breast cancer requesting bilateral risk-reducing mastectomy (BRRM)

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Multidisciplinary Care of the High-Risk Individual

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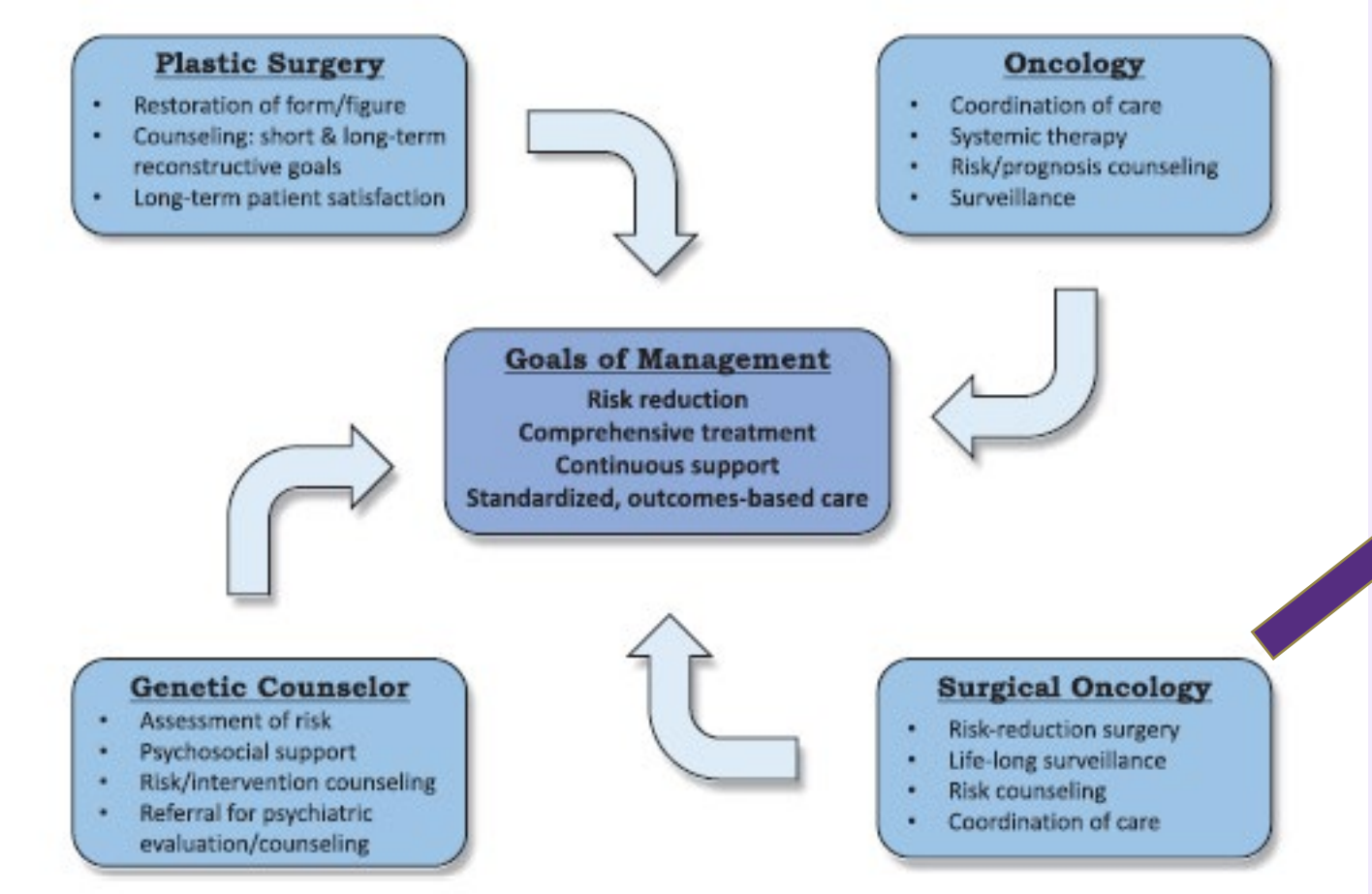
Current Role of The Breast Surgeon

RISK ASSESSMENT TREATMENT

RISK MANAGEMENT

BREAST CANCER



Surgical Oncology

- Risk-reduction surgery ✓
- Life-long surveillance ✗
- Risk counseling ✗
- Coordination of care ✗

Unsustainable

- Workload
- Manpower
- Inappropriate use of surgical time /expertise

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RISK ASSESSMENT

RISK MANAGEMENT

HIGH-RISK / ENHANCED SCREENING

- Clinical Breast Examination (CBE)
- Breast Imaging incl MRI (or ? CEM) /3D mammography +/- ultrasound

RISK-REDUCTION

Non-Surgical

- Lifestyle Modification
- Risk-Reducing Medication

Surgical

- Risk-Reducing Surgery – Bilateral Risk-Reducing Mastectomy (BRRM)

BREAST CANCER TREATMENT

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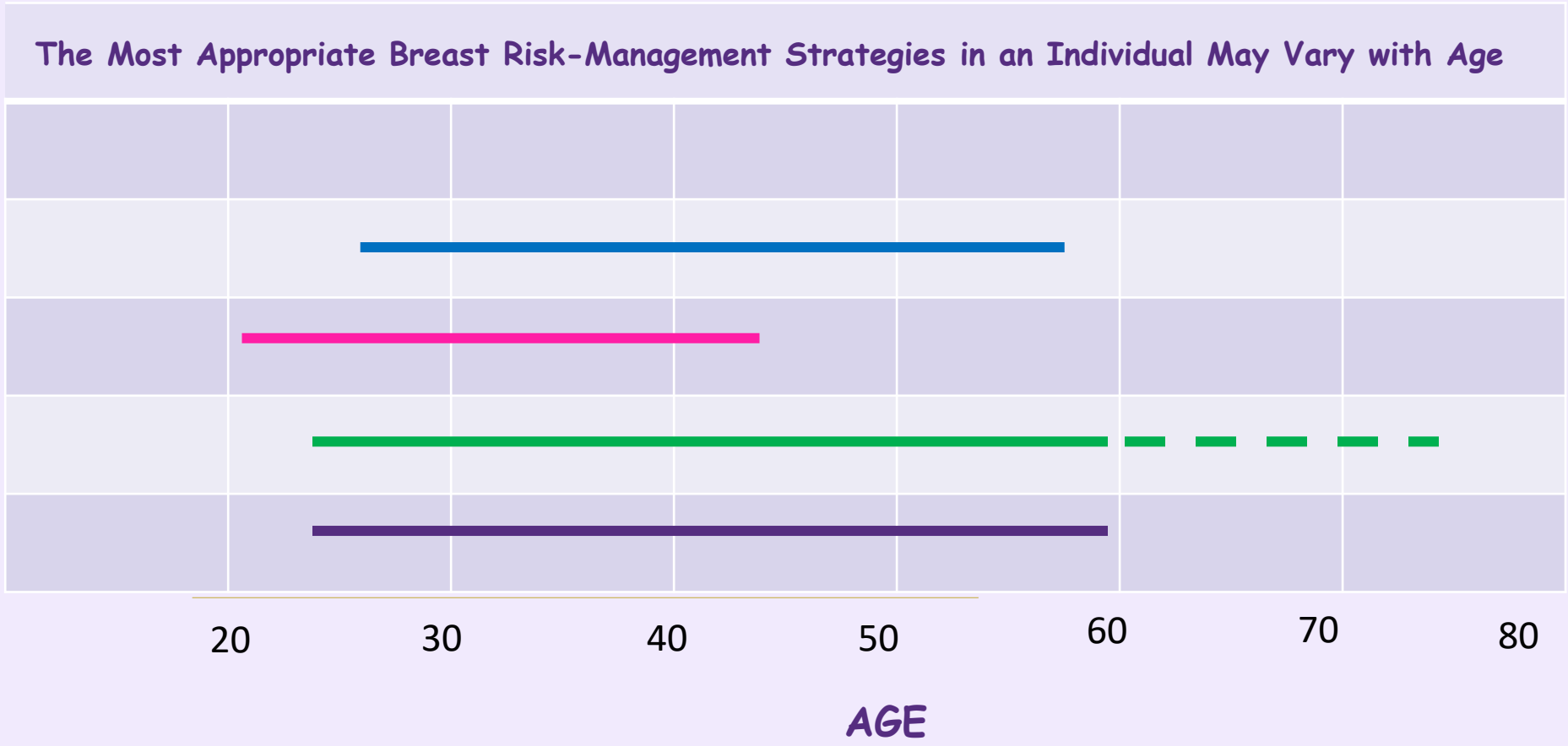
The Most Appropriate Breast Risk-Management Strategies in an Individual May Vary with Age



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RISK MANAGEMENT

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HIGH-RISK / ENHANCED SCREENING

- Clinical Breast Examination (CBE) – v limited role - ? consider during pregnancy / lactation
- Breast Imaging incl MRI/3D mammography +/- ultrasound – sl reduction in mortality demonstrated with MRI screening when compared with no MRI screening

RISK-REDUCTION

Non-Surgical

- Lifestyle Modification – exercise /weight control- same relative RR as in average risk individuals / no conclusive evidence wrt HRT/alcohol
- Risk-Reducing Medication – 38% risk reduction BC from meta-analysis of trials / no survival benefit

Surgical

- Risk-Reducing Surgery – Bilateral Risk-Reducing Mastectomy (BRRM) -90-100% BC risk reduction, but definite evidence of survival benefit has been more difficult to demonstrate
- Degree of Risk Reduction not influenced by the nature of mastectomy +/- reconstruction

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High-Risk Individual

TREATMENT OF BREAST CANCER

- BCT: Germline BRCA status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast conserving therapy (BCT) from receiving BCT

However

- Surgical management of the index malignancy (BCT vs ipsilateral therapeutic and contralateral risk-reducing mastectomy [CRRM]) should be discussed in BRCA1/2 mutation carriers, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer, compared with noncarriers

Management of Hereditary Breast Cancer in BRCA1/2 (ASCO)

Women with breast cancer who have a *BRCA1/2* mutation	
Local therapy recommendations	
Index/current cancer	Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for BCT from receiving BCT.
	Surgical management of the index malignancy (BCT *v* ipsilateral therapeutic and CRRM) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers.
	For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in *BRCA1/2*, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients.
	For women with breast cancer who are treated with BCT or with mastectomy for whom postmastectomy RT is considered, RT should not be withheld because of mutation status, except for mutations in *TP53* (see Recommendation 6.3, which states that irradiation of the intact breast is contraindicated in *TP53* carriers). There is no evidence of a significant increase in toxicity or CBC related to radiation exposure among patients with a mutation in a *BRCA1/2*
Contralateral risk-reducing mastectomy (CRRM)	For women with breast cancer who have a BRCA1/2 mutation, CRRM should be discussed. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and the role of risk-reducing mastectomy: -Age at diagnosis (the strongest predictor of future contralateral breast cancer) -Family history of breast cancer -Overall prognosis from this or other cancers (eg, ovarian) -Ability of patient to undergo appropriate breast surveillance (MRI) -Comorbidities -Life expectancy
	For patients with breast cancer with a deleterious germline *BRCA1/2* mutation interested in risk-reducing contralateral mastectomy, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option.
	BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI.

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J Clin Oncol 38: 2080-2106 2020

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BREAST CANCER TREATMENT IN THE HIGH-RISK INDIVIDUAL

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Surgical Treatment of Breast Cancer in the patient with a known or suspected germline mutation in a breast cancer susceptibility gene

Surgical Options for Women with Unilateral Breast Cancer Suitable for Breast Conserving Surgery (BCS)

- Breast Conserving Therapy (BCT) = Breast Conserving Surgery (BCS) + Whole Breast Radiotherapy (WBRT)
- Bilateral Mastectomy (Unilateral Therapeutic Mastectomy + Contralateral Risk-Reduction Mastectomy (CRRM) +/- reconstruction
- Unilateral Mastectomy +/- reconstruction. ✖
- Staged Surgery: BCS / Chemotherapy
  - → WBRT
  - → Bilateral Mastectomy +/- reconstruction

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Surgical Options for Women with Unilateral Breast Cancer NOT Suitable for Breast Conserving Surgery (BCS)

- Unilateral Mastectomy +/- reconstruction
- Bilateral Mastectomy +/- reconstruction

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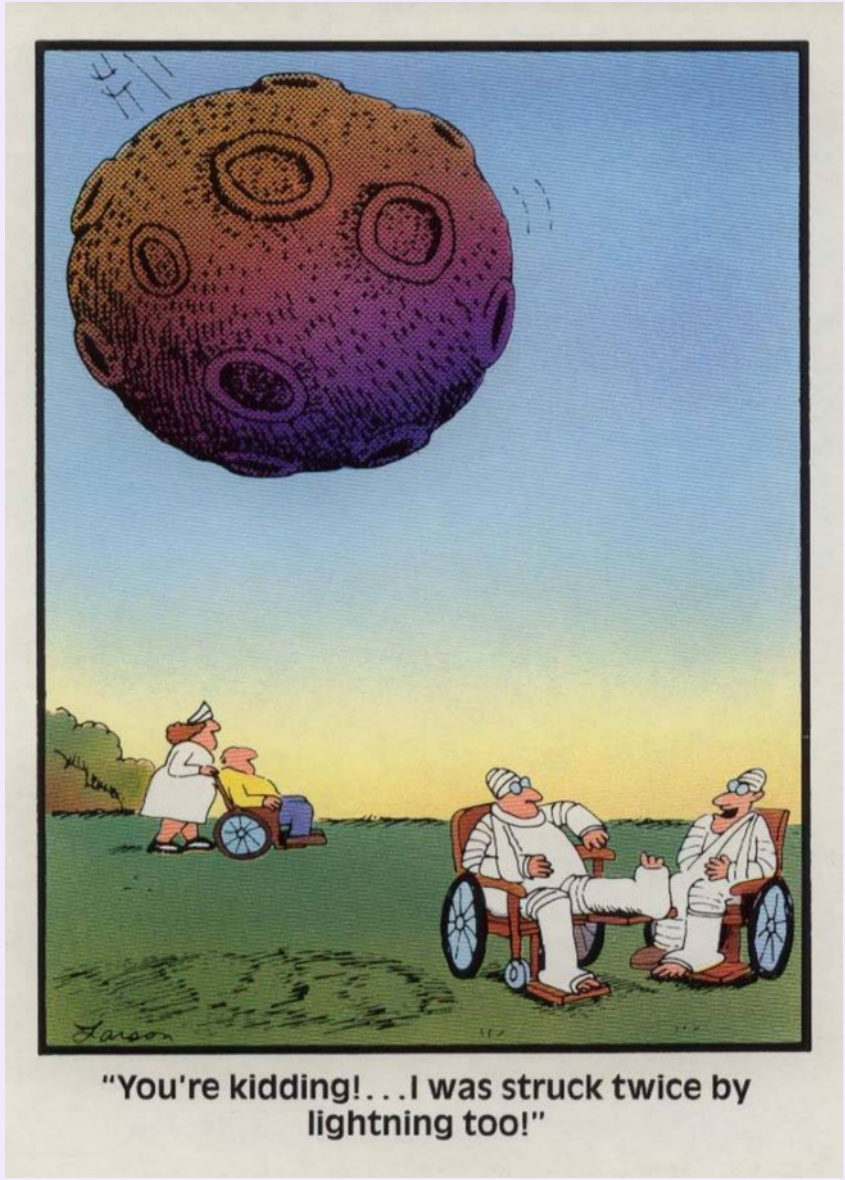

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Women with hereditary breast cancer are at increased risk of second primary ipsilateral and contralateral breast cancers

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Treatment

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- BRCA1 and BRCA2 mutations are associated with both an extremely high risk of development of a first breast cancer, as well as a markedly elevated risk of subsequent ipsilateral and contralateral cancers.

- In a cohort study of 3886 women, the cumulative risk of contralateral breast cancer (CBC) 20 years after a first breast cancer diagnosis was **40%** for BRCA1 carriers and **26%** for BRCA2 carriers **(Kuchenbaeker et al, JAMA 2017 Volume 317, Number 23)**

The level of risk varies with:

- mutation
- age at first breast cancer diagnosis

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- Patients with newly diagnosed breast cancer (BC) and BRCA1/2 mutations may be considered for breast conserving therapy (BCT), with local control of the index cancer ***similar*** to that of noncarriers.

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Local recurrence rates after BCT and mastectomy in BRCA mutation carriers.

Years after Surgery	Median % Local Recurrence (Range)			
	BCT		Mastectomy	
5	13.3% (2.0–22.0)	N = 1212	5.2% (1.4–9.0)	N = 470
10	16.2% (10.5–52.0)	N = 1566	7.3% (5.5–9.0)	N = 470
15	23.8% (15.8–49.0)	N = 1085	7.3% (5.5–9.4)	N = 470

Data from Co M. et al. [6] BCT: breast-conserving therapy.

- The significant risk of a contralateral BC (CBC), especially in young women, and the higher risk of new cancers in the ipsilateral breast warrant discussion of bilateral mastectomy.
- Patients with mutations in moderate-risk genes should be offered BCT.
- For women with mutations in BRCA1/2 or moderate-penetrance genes who are eligible for mastectomy, nipple-sparing mastectomy is a reasonable approach.
- There is no evidence of increased toxicity or CBC events from radiation exposure in BRCA1/2 carriers.
- Radiation therapy should not be withheld in ATM carriers.
- For patients with germline TP53 mutations, mastectomy is advised; radiation therapy is contraindicated except in those with significant risk of locoregional recurrence

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The following factors should be considered for assessing risk of Contralateral Breast Cancer (CBC) and the role of RRM in BRCA Carriers

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- age at diagnosis (the strongest predictor of future CBC)
- family history of breast cancer
- overall prognosis from this or other cancers (eg, ovarian)
- Comorbidities
- life expectancy
- Ability of patient to undergo appropriate breast surveillance (MRI). BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual MRI/mammogram.

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Role of Contralateral Risk-Reduction Mastectomy (CRRM)

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- Following a diagnosis of breast cancer, high-risk patients have a 2–3% per year risk of breast cancer—constant for almost 3 decades.

- Those whose breast cancer was diagnosed before the age of 40 years are at particularly heightened risk and potentially benefit most from risk-reducing strategies.

- Netherlands study (**Int. J. Cancer: 136, 668–677, 2015)** showed a survival benefit from CRRM amongst BRCA mutation carriers.

Greatest survival benefit was derived amongst women:

- Diagnosed before the age of 40 years
- Not having chemotherapy
- Favourable histology (Grade 1/2 cancers and non-triple negative status).
- CRRM may half the risk of death from breast cancer over a 20-year period

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- When discussing contralateral prophylactic mastectomy with BRCA1/2 mutation carriers, it is essential to provide patients with their ***absolute*** risk of CBC.

- The younger the age at first breast cancer diagnosis, the higher the absolute risk of subsequent CBC.

- For example, at 25 years, the absolute risk of CBC for BRCA2 carriers diagnosed before age 40 years is 68% versus 20% if diagnosed at age 50 years.

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Risk-Reducing Strategies

Assessment of Efficacy depends on the Endpoint

1 Risk management strategies for breast and ovarian* cancers in *BRCA1* and *BRCA2* mutation carriers

Strategy	Relative risk reduction	
	Breast cancer	Ovarian cancer
Risk-reducing mastectomy	> 90%	—
Risk-reducing bilateral salpingo-oophorectomy	Up to 50% (if premenopausal)	> 90%
Risk-reducing medication	38%† (tamoxifen/raloxifene)	About 50%‡ (oral contraceptive pill)
Screening	0 (mammography/MRI)	0 (ultrasound/Ca125)§
Tubal ligation	—	About 40%

* High-grade serous cancers of the ovary, fallopian tube or peritoneum. † Estimate from meta-analysis of multiple randomised controlled trials in high-risk women; limited data suggest a similar benefit in mutation carriers. ‡ The effects of the oral contraceptive pill on breast cancer risk are uncertain. § Ineffective and not recommended.[2]

MJA 199 (10) · 18 November 2013

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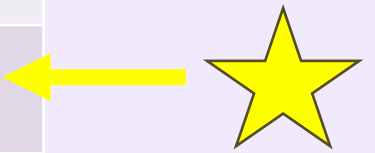
If the endpoint is reducing the **risk of developing breast cancer**

Intervention	Relative Reduction in Breast Cancer Risk
Screening (enhanced or otherwise)	**** ZERO ****
Risk-Reducing Medication	38% (25—50%)
Risk-Reducing Mastectomy	90% at least (95-100% in recent series)



HOWEVER

If the endpoint is avoiding **death from breast cancer**

Intervention	Overall Breast Cancer Survival
Enhanced Screening with MRI	Sl reduction in mortality
Risk-Reducing Medication	N/A
Risk-Reducing Mastectomy	Sl reduction in mortality, mainly in BRCA1

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Is prevention always better than cure?

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"Every breast or ovarian cancer patient with a BRCA1 or BRCA2 mutation detected after diagnosis is a missed opportunity to prevent a cancer.

No woman with a BRCA1 or BRCA2 mutation should die from breast or ovarian cancer"

Mary Claire King

"Every breast or ovarian cancer diagnosed in a known BRCA mutation carrier represents a failure of risk-management"

Breast Cancer Risk Management Guidelines for High-Risk Individuals

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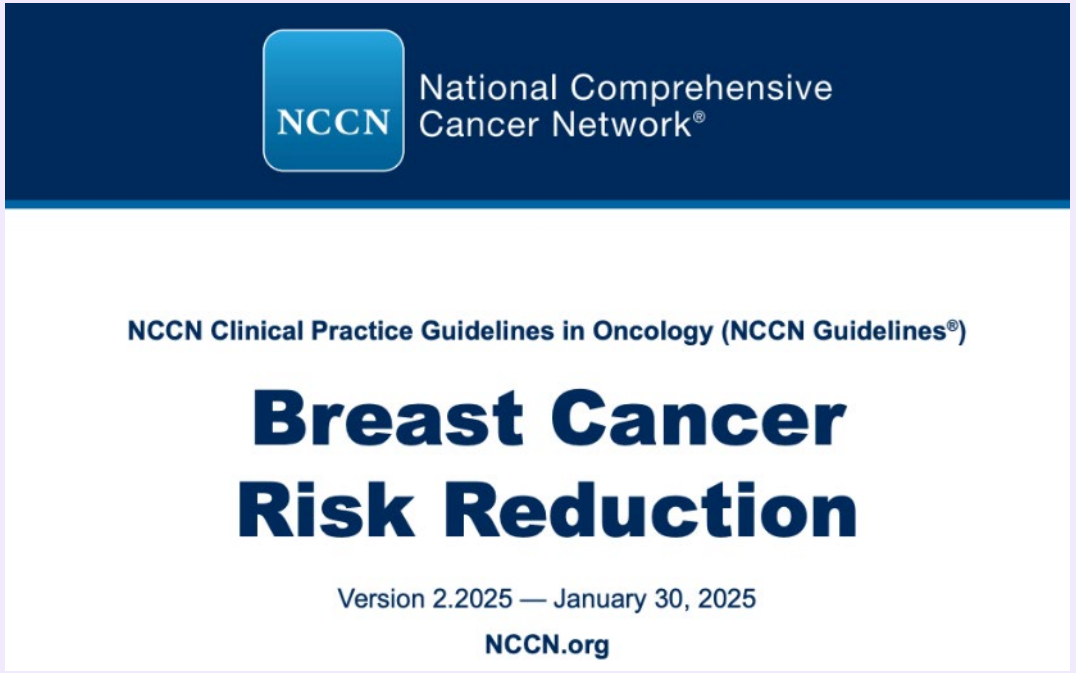
NSW GOVERNMENT | eviQ

BRCA1 or BRCA2 – risk management (female)

Breast cancer (high risk with no family history of ovarian cancer) – risk management (female)

www. eviq.org.au



2025

www.nccn.org

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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
Last updated: 14 November 2023

www.nice.org.uk/guidance/cg164

2024

www.nice.org.uk

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline☆

C. Sessa[1], J. Balmaña[2], S. L. Bober[3], M. J. Cardoso[4], N. Colombo[5,6], G. Curigliano[7,8], S. M. Domchek[9], D. G. Evans[10,11], D. Fischerova[12], N. Harbeck[13], C. Kuhl[14], B. Lemley[15,16], E. Levy-Lahad[17], M. Lambertini[18,19], J. A. Ledermann[20], S. Loibl[21], K.-A. Phillips[22] & S. Paluch-Shimon[23], on behalf of the ESMO Guidelines Committee*

2024

www.esmo.org

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Risk-Reducing Mastectomy

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Society of Surgical Oncology Breast Disease Working Group Statement on Prophylactic (Risk-Reducing) Mastectomy

Kelly K. Hunt, MD[1], David M. Euhus, MD[2], Judy C. Boughey, MD[3], Anees B. Chagpar, MD[4], Sheldon M. Feldman, MD[5], Nora M. Hansen, MD[6], Swati A. Kulkarni, MD[6], David R. McCready, MD[7], Eleftherios P. Mamounas, MD[8], Lee G. Wilke, MD[9], Kimberly J. Van Zee, MD[10], and Monica Morrow, MD[10]

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Ann Surg Oncol (2017) 24:375–397

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Contralateral Risk-Reduction Mastectomy (CRRM) Guidelines

The Breast Centre
thebreastcentre.com.au

Ann Surg Oncol (2017) 24:1–2
DOI 10.1245/s10434-016-5648-7

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

CrossMark

EDITORIAL – BREAST ONCOLOGY

Guidelines for Guidelines: An Assessment of the American Society of Breast Surgeons Contralateral Prophylactic Mastectomy Consensus Statement

Todd M. Tuttle, MD[1], Andrea V. Barrio, MD[2], V. Suzanne Klimberg, MD[3], Armando E. Giuliano, MD[4], Mariana Chavez-MacGregor, MD[5], Heather A. Thompson Buum[6], and Kelly M. McMasters, MD, PhD[7]

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2017

Ann Surg Oncol
DOI 10.1245/s10434-016-5443-5

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Contralateral Prophylactic Mastectomy (CPM) Consensus Statement from the American Society of Breast Surgeons: Data on CPM Outcomes and Risks

Judy C. Boughey, MD[1], Deanna J. Attai, MD[2], Steven L. Chen, MD, MBA[3], Hiram S. Cody, MD[4], Jill R. Dietz, MD[5], Sheldon M. Feldman, MD[6], Caprice C. Greenberg, MD, MPH[7], Rena B. Kass, MD[8], Jeffrey Landercasper, MD[9], Valerie Lemaine, MD, MPH[1], Fiona MacNeill, MB, BS[10], David H. Song, MD[11], Alicia C. Staley, BS, MBA, MS[12], Lee G. Wilke, MD[7], Shawna C. Willey, MD[13], Katharine A. Yao, MD[14], and Julie A. Margenthaler, MD[15]

2016

Ann Surg Oncol (2016) 23:3106–3111
DOI 10.1245/s10434-016-5408-8

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

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Contralateral Prophylactic Mastectomy Consensus Statement from the American Society of Breast Surgeons: Additional Considerations and a Framework for Shared Decision Making

Judy C. Boughey, MD[1], Deanna J. Attai, MD[2], Steven L. Chen, MD, MBA[3], Hiram S. Cody, MD[4], Jill R. Dietz, MD[5], Sheldon M. Feldman, MD[6], Caprice C. Greenberg, MD[7], Rena B. Kass, MD[8], Jeffrey Landercasper, MD[9], Valerie Lemaine, MD, MPH[1], Fiona MacNeill, MD[10], Julie A. Margenthaler, MD[11], David H. Song, MD[12], Alicia C. Staley, BS, MBA, MS[13], Lee G. Wilke, MD[7], Shawna C. Willey, MD[14], and Katharine A. Yao, MD[15]

2016

RESEARCH Open Access

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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]

Abstract

Background: Rates of contralateral risk-reducing mastectomy (CRRM) are rising, despite a decreasing global incidence of contralateral breast cancer. Reasons for requesting this procedure are complex, and we have previously shown a variable practice amongst breast and plastic surgeons in England. We propose a protocol, based on a published systematic review, a national UK survey and the Manchester experience of CRRM.

Methods: We reviewed the literature for risk factors for contralateral breast cancer and have devised a 5-step process that includes history taking, calculating contralateral breast cancer risk, cooling off period/counselling, multi-disciplinary assessment and consent. Members of the multi-disciplinary team included the breast surgeon, plastic surgeon and geneticist, who formulated guidelines.

Results: A simple formula to calculate the life-time risk of contralateral breast cancer has been devised. This allows stratification of breast cancer patients into different risk-groups: low, above average, moderate and high risk. Recommendations vary according to different risk groups.

Conclusion: These guidelines are a useful tool for clinicians counselling women requesting CRRM. Risk assessment is mandatory in this group of patients, and our formula allows evidence-based recommendations to be made.

Keywords: Contralateral, Breast cancer, Risk-reducing mastectomy, Guidelines, Multi-disciplinary team

2015

Review

EBCC-13 manifesto: Balancing pros and cons for contralateral prophylactic mastectomy

Marjanka K. Schmidt [a,b,*], Jennifer E. Kelly [c], Anne Brédart [d,e], David A. Cameron [f], Jana de Boniface [g,h], Douglas F. Easton [i,j], Birgitte V. Offersen [k], Fiorita Poulakaki [l,m], Isabel T. Rubio [n], Francesco Sardanelli [o,p], Rita Schmutzler [q], Tanja Spanic [m,r], Britta Weigelt [s], Emiel J.T. Rutgers [t]

2023

Ann Surg Oncol (2024) 31:2212–2223
https://doi.org/10.1245/s10434-024-14893-x

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

REVIEW ARTICLE – BREAST ONCOLOGY

Society of Surgical Oncology Breast Disease Site Working Group Statement on Contralateral Mastectomy: Indications, Outcomes, and Risks

Puneet Singh, MD, MS[1], Doreen Agnese, MD[2], Miral Amin, MD[3], Andrea V. Barrio, MD[4], Astrid Botty Van den Bruele, MD[5], Erin Burke, MD[6], David N. Danforth Jr., MD[7], Frederick M. Dirbas, MD[8], Firas Eladoumikdachi, MD[9], Olga Kantor, MD[10], Shicha Kumar, MD[11], Marie Catherine Lee, MD[12], Cindy Matsen, MD[13], Toan T. Nguyen, MD[14], Tolga Ozmen, MD[15], Ko Un Park, MD[10], Jennifer K. Plichta, MD, MS[5], Chantal Reyna, MD[16], Shayna L. Showalter, MD[17], Toncred Styblo, MD[18], Nicholas Tsanakas, MD[19], Anna Weiss, MD[20], Christine Laronga, MD[12], and Judy Boughey, MD[21]

2024

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Breast Cancer Treatment Guidelines for High-Risk Individuals

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ASCO special articles

Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline

Nadine M. Tung, MD[1]; Judy C. Boughey, MD[2]; Lori J. Pierce, MD[3]; Mark E. Robson, MD[4]; Isabelle Bedrosian, MD[5]; Jill R. Dietz, MD[6]; Anthony Dragun, MD[7]; Judith Balmana Gelpi, MD, PhD[8]; Erin W. Hofstatter, MD[9]; Claudine J. Isaacs, MD[10]; Ismail Jatoi, MD, PhD[11]; Elaine Kennedy[12]; Jennifer K. Litton, MD[5]; Nina A. Mayr, MD[13]; Rubina D. Qamar, MD[14]; Mark G. Trombetta, MD[15]; Brittany E. Harvey, BS[16]; Mark R. Somerfield, PhD[16]; and Dana Zakalik, MD[17]

J Clin Oncol 38:2080-2106 2020

PURPOSE To develop recommendations for management of patients with breast cancer (BC) with germline mutations in BC susceptibility genes.

METHODS The American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology convened an Expert Panel to develop recommendations based on a systematic review of the literature and a formal consensus process.

RESULTS Fifty-eight articles met eligibility criteria and formed the evidentiary basis for the local therapy recommendations; six randomized controlled trials of systemic therapy met eligibility criteria.

RECOMMENDATIONS Patients with newly diagnosed BC and *BRCA1/2* mutations may be considered for breast-conserving therapy (BCT), with local control of the index cancer similar to that of noncarriers. The significant risk of a contralateral BC (CBC), especially in young women, and the higher risk of new cancers in the ipsilateral breast warrant discussion of bilateral mastectomy. Patients with mutations in moderate-risk genes should be offered BCT. For women with mutations in *BRCA1/2* or moderate-penetrance genes who are eligible for mastectomy, nipple-sparing mastectomy is a reasonable approach. There is no evidence of increased toxicity or CBC events from radiation exposure in *BRCA1/2* carriers. Radiation therapy should not be withheld in *ATM* carriers. For patients with germline *TP53* mutations, mastectomy is advised; radiation therapy is contraindicated except in those with significant risk of locoregional recurrence. Platinum agents are recommended versus taxanes to treat advanced BC in *BRCA* carriers. In the adjuvant/neoadjuvant setting, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. Poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) are preferable to nonplatinum single-agent chemotherapy for treatment of advanced BC in *BRCA1/2* carriers. Data are insufficient to recommend PARP inhibitor use in the early setting or in moderate-penetrance carriers. Additional information available at www.asco.org/breast-cancer-guidelines.

www.asco.org

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RISK ASSESSMENT

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Input of genetics specialist/counsellor invaluable

Clinician responsible for long term risk management must also be aware of risk levels, esp changes over time

Several validated risk evaluators available:

- iPrevent https://www.petermac.org/iprevent or https://iprevent.net.au
- CanRisk https://www.canrisk.org/
- Tyrer-Cuzick (IBIS Tool) http://www.ems-trials.org/riskevaluator/
- BCSC https://tools.bcsc-scc.ucdavis.edu/BC5yearRisk/#calculator

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The various risk evaluation models have sl different breast cancer risk factor inputs which include:

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- Reproductive factors- menarche, age at first birth, parity, menopause, HRT use
- Lifestyle factors – BMI, exercise, alcohol
- History of previous breast disease, particularly lobular carcinoma in situ LCIS) or atypical hyperplasia (ADH/ALH)
- Family history breast, ovarian cancer, including age at diagnosis
- Gene test result- iPrevent / IBIS BRCA 1 / 2 only, CanRisk includes additional genetic variants such as PALB2, CHEK2 and ATM
- Mammographic breast density

- Models variously calculate 5, 10 and residual lifetime invasive breast cancer risks
- Results expressed as graphs +/- pictograms
- Individual's risk is compared to that of an average risk woman of the same age, using age specific breast cancer rates
- Tyrer-Cuzick and CanRisk calculate mutation carrier probability of BRCA 1/2
- CanRisk calculates mutation carrier probabilities in breast and ovarian cancer susceptibility genes in addition to BRCA1/2 (PALB2, CHEK2, ATM RAD51C, RAD51D, BRIP1)

***CanRisk suitable for use in individuals with a breast cancer diagnosis**

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iPrevent

https://iprevent.net.au

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After calculating breast cancer risk, iPrevent presents screening and risk-reduction and options appropriate to the estimated risk, based on Australian guidelines.

Options presented may include:

- Breast cancer screening
- Bilateral Risk-Reducing Mastectomy,
- Risk -Reducing medication, such as tamoxifen
- Lifestyle modifications, such as weight loss and reducing alcohol intake

The estimated risk reduction afforded by these strategies is applied according to the following:

- Risk reducing mastectomy – 90% reduction
- Five years of tamoxifen– 33% reduction
- Five years of raloxifene – 25% reduction
- Five year of exemestane or anastrazole use – a 50% reduction is applied

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Example:

- 25 yo, Unaffected BRCA1 carrier

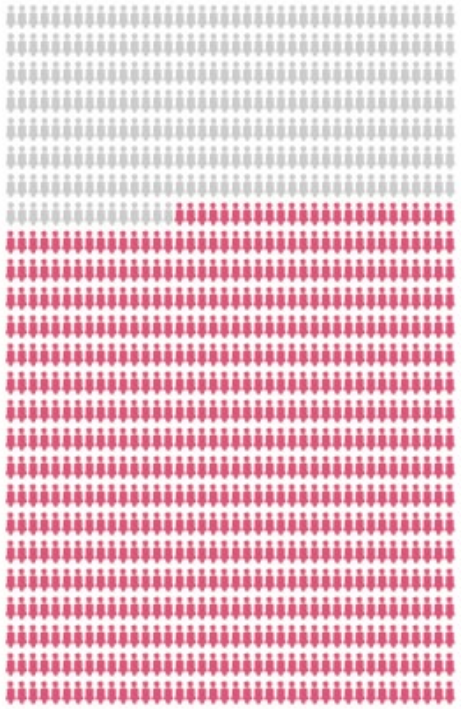
Your Risk Over the Rest of Your Life

Your risk of developing breast cancer over the rest of your life is 70.5%. This means 705 out of 1000 women your age, with the same risk of breast cancer as you, will develop breast cancer at some time in their life.

The risk for an average woman of your age is 11.8%. This means 118 out of 1000 women of your age, at average risk in the general population, will develop breast cancer at some time in their life.

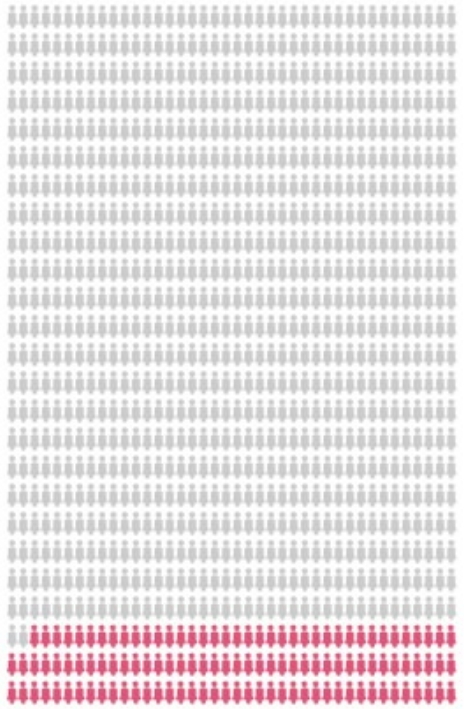
Your risk

Your lifetime risk:
295 women will not get breast cancer
705 women will get breast cancer



Population risk

Average lifetime risk:
882 women will not get breast cancer
118 women will get breast cancer



The diagram on the left represents 1000 women your age with the same risk of breast cancer as you. You can compare that with the diagram on the right which represents 1000 women your age with an average breast cancer risk.

Out of 1000 women of your age, 705 will develop breast cancer at some time in their lives, compared with 118 women who are of average risk.

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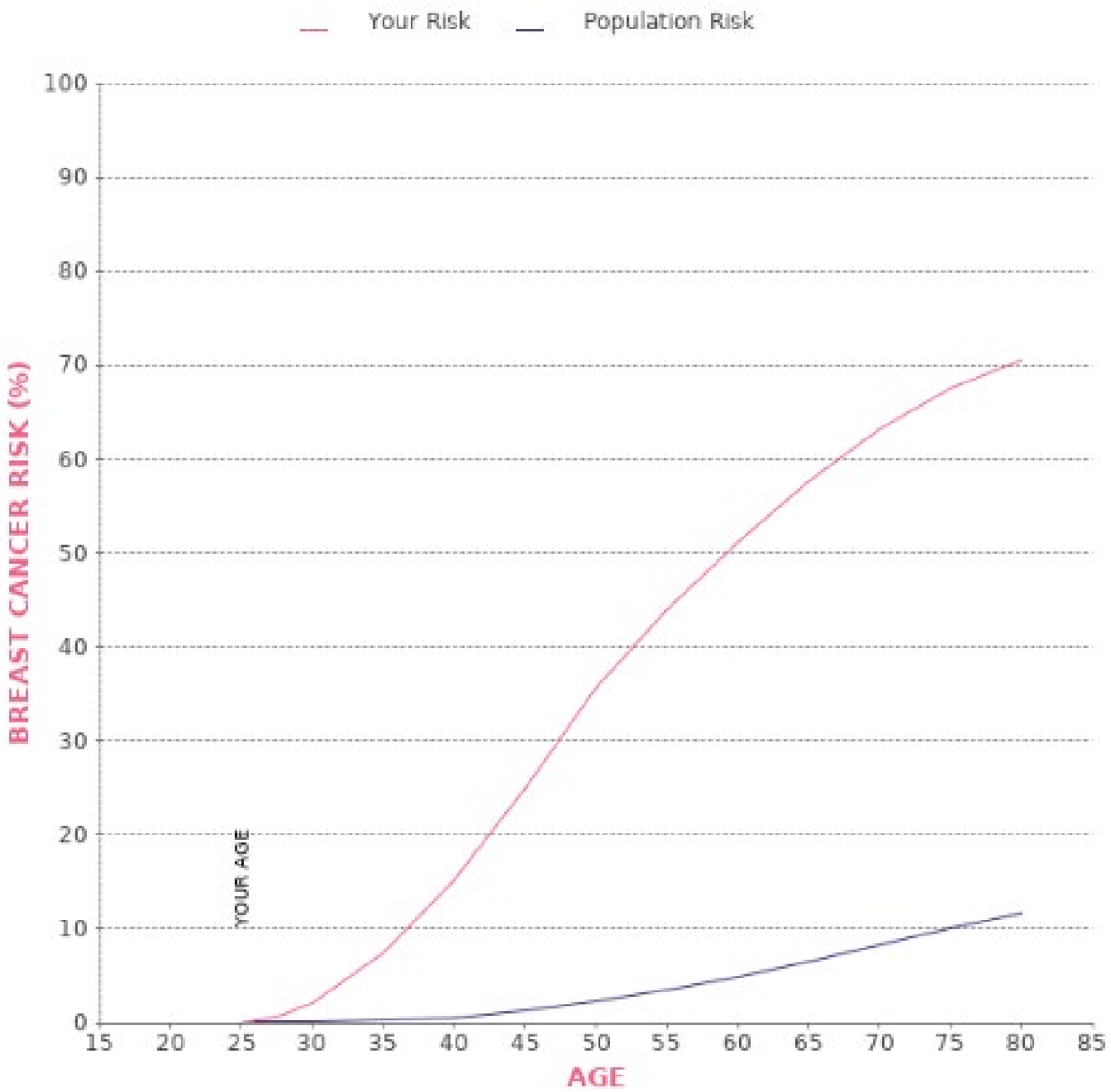

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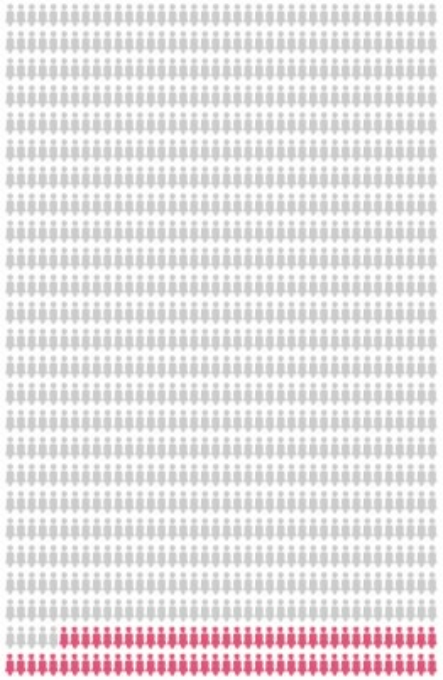
Your risk in the next 10 years

Your risk of developing breast cancer over the next ten years is 7.5%. This means that 75 out of 1000 women your age, with the same risk of breast cancer as you, will develop breast cancer in the next ten years.

The risk for an average woman of your age is 0.2%. This means that 2 out of 1000 women your age, at average risk in the general population, will develop breast cancer in the next ten years.

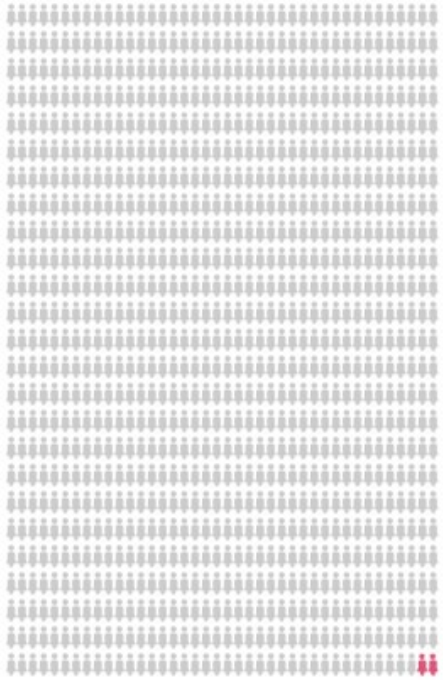
Your risk

Your risk over next ten years:
925 women will not get breast cancer
75 women will get breast cancer



Population risk

Average risk over next ten years:
998 women will not get breast cancer
2 women will get breast cancer



The diagram on the left represents 1000 women your age with the same risk of breast cancer as you. You can compare that with the diagram on the right which represents 1000 women your age with an average breast cancer risk.

Out of 1000 women your age, 75 will get breast cancer in the next 10 years, compared with 2 women who are at average risk in the general population.

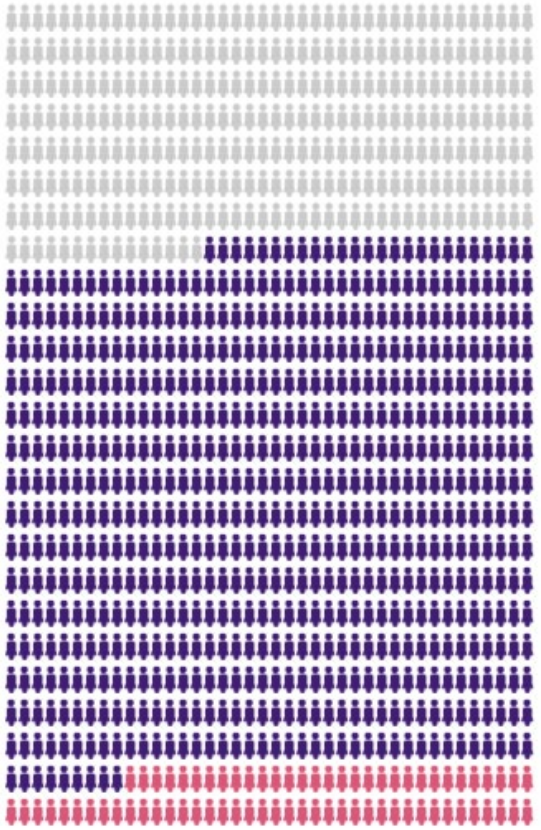
Reduction in your risk over your lifetime

Risk reducing mastectomy will reduce your risk of developing invasive breast cancer over **the rest of your life** from 70.5% to 7.1%.

Over the same time, the breast cancer risk for an average woman of your age is 11.8%.

This means that if 1000 women with the same risk of breast cancer as you all had the operation, 71 would get breast cancer over the rest of their lives. However if none of the 1000 women had the operation 705 would get breast cancer. So by having the operation breast cancer would have been prevented in 634 women.

295 women will not get breast cancer regardless
634 women will not get breast cancer because of the surgery
71 women will get breast cancer even with the surgery



This diagram represents 1000 women with the same risk of breast cancer as you. Many women (in grey here) will not develop breast cancer over their lifetime regardless of whether or not they have the operation. Some women (in purple here) will not develop breast cancer over their lifetime because of the operation. Some women (in pink outline here) will develop breast cancer over their lifetime even if they have the operation. The women in purple represent those who avoid breast cancer if 1000 women like you have the operation.

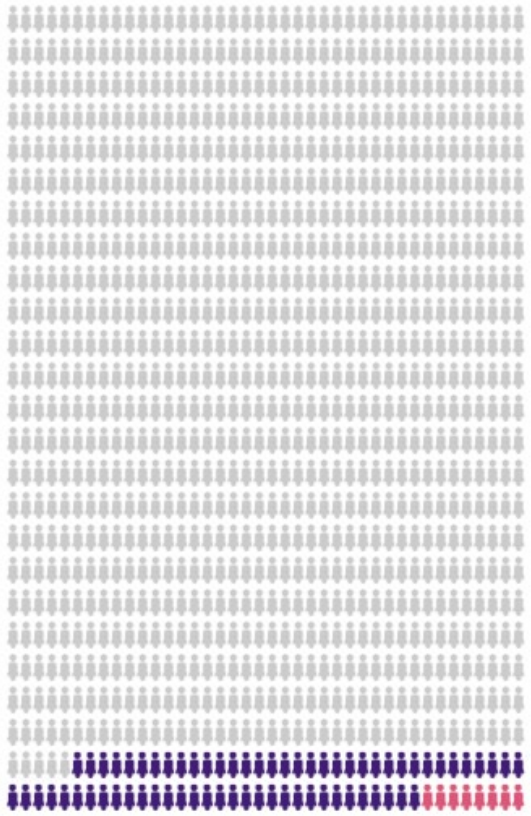
Reduction in your risk over next 10 years

Risk reducing mastectomy will reduce your risk of developing invasive breast cancer over the next **10 years** from 7.5% to 0.8%.

Over the same time, the risk for an average woman of your age is 0.2%.

This means that if 1000 women with the same risk of breast cancer as you all had the operation, 8 would develop breast cancer in the next 10 years. However if none of the 1000 women had the operation 75 would get breast cancer. So by having the operation breast cancer would have been prevented in 67 women.

925 women will not get breast cancer regardless
67 women will not get breast cancer because of the surgery
8 women will get breast cancer even with the surgery



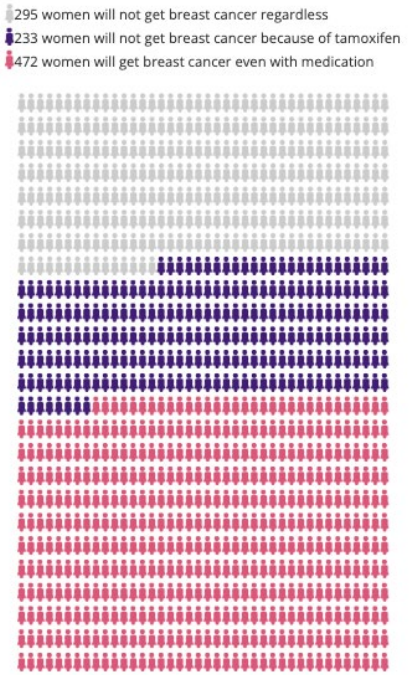
This diagram represents 1000 women with the same risk of breast cancer as you. Many women (in grey here) will not develop breast cancer over the next 10 years regardless of whether or not they have the operation. Some women (in purple here) will not develop breast cancer over the next 10 years because of the operation. Some women (in pink here) will develop breast cancer over the next 10 years even if they have the operation. The women in purple represent those who avoid breast cancer if 1000 women like you have the operation.

Risk of breast cancer over the rest of your life with tamoxifen:

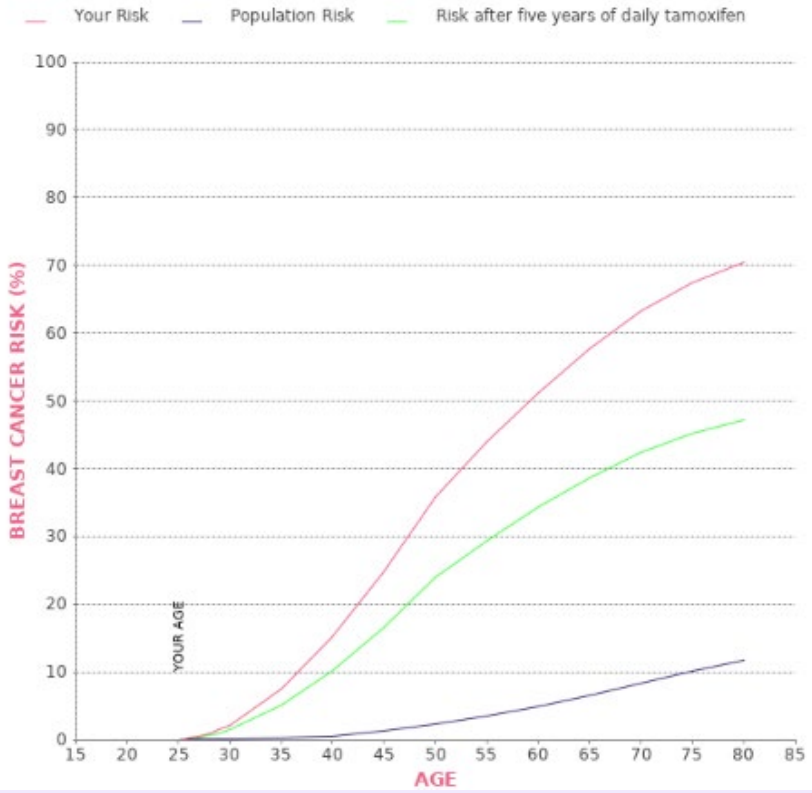
Tamoxifen will reduce your risk of developing breast cancer over your lifetime from 70.5% to 47.2%.

Over the same time, the risk for an average woman of your age is 11.8%.

This means that if we take 1000 women with the same risk of breast cancer as you all took 5 years of tamoxifen, 472 would develop breast cancer over the rest of their lives. However if none of the 1000 women took tamoxifen 705 would get breast cancer. Breast cancer would have been prevented in 233 women.



This diagram represents 1000 women with the same risk of breast cancer as you. Many women (in grey here) will not develop breast cancer over their lifetime regardless of whether or not they take the tamoxifen. Some women (in purple here) will not develop breast cancer over their lifetime because take the tamoxifen. Some women (in pink here) will develop breast cancer over their lifetime even if they take the tamoxifen. The women in purple represent those who avoid breast cancer if 1000 women like you take the tamoxifen.



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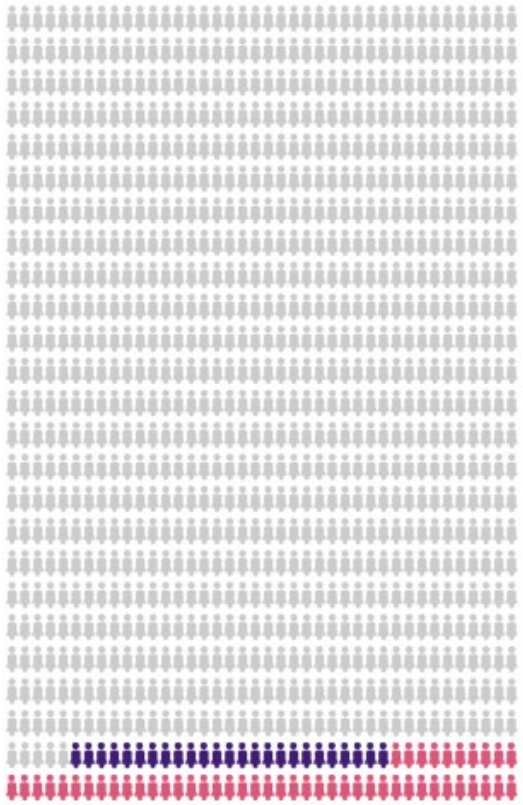
Risk of breast cancer over next ten years with tamoxifen:

Tamoxifen will reduce your risk of developing breast cancer over the next ten years from 7.5% to 5.0%.

Over the same time, the risk for an average woman of your age is 0.2%.

This means that if 1000 women with the same risk of breast cancer as you all took 5 years of tamoxifen, 50 would develop breast cancer in the next 10 years. However if none of the 1000 women took the medication 75 would get breast cancer. Breast cancer would have been prevented in 25 women.

925 women will not get breast cancer regardless
25 women will not get breast cancer because of tamoxifen
50 women will get breast cancer even with medication



This diagram represents 1000 women with the same risk of breast cancer as you. Many women (in grey here) will not develop breast cancer over the next ten years regardless of whether or not they take medication. Some women (in purple here) will not develop breast cancer over the next ten years because they take medication. Some women (in pink here) will develop breast cancer over the next ten years even if they take medication. The women in green represent those who avoid breast cancer if 1000 women like you take medication.

Lifestyle Measures

Changing your lifestyle may help reduce your breast cancer risk. Some of these things may not be relevant to you currently, but they may become relevant in the future.

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Exercise

You currently do at least 30 minutes of moderate-intensity exercise every day, this is recommended by Cancer Australia to reduce your cancer risk. Moderate-intensity exercise examples include brisk walking, jogging, running, medium- to fast-paced swimming, cycling, aerobics, and some group sports. The more you exercise, the greater the reduction in breast cancer risk.

It is recommended that you continue to do at least 30 minutes of moderate-intensity exercise every day.

Alcohol

On average, you consume 0 standard drinks of alcohol per week (click here to review how many standard drinks you have). Drinking even one alcoholic drink per day increases your risk for breast cancer and other diseases. The more you drink, the greater the increase in risk.

National guidelines recommend you have no more than two standard drinks a day.

Weight

Your body mass index (BMI) is calculated from your weight and height. It can determine if you are underweight, a healthy weight, overweight, or obese.

Your BMI is 21.4. This indicates you are a healthy weight. After the menopause, being overweight increases the risk of breast cancer.

It is recommended that you maintain a healthy weight. Your target healthy weight is below 64.0 kg.

Pregnancies

The more children you have, and the earlier you have them, the lower your risk of breast cancer.

Breast feeding

Breast feeding can decrease your risk of breast cancer. National guidelines recommend breast feeding each child for at least 12 months if you can.

Hormonal Contraception

Breast cancer risk is increased while you are using a hormonal contraceptive such as the contraceptive pill, implant, Mirena IUD, or depot injection. There may also be a risk for some years after stopping it. The size of the increased risk due to hormonal contraception depends on your underlying breast cancer risk and must be balanced against the benefits of using the contraception. If you are young (e.g. in your 20s), even if your underlying breast cancer risk is high, any increase in risk due to using hormonal contraception is likely quite small - especially if it is not used for a long time. You should discuss this, and the range of alternative contraceptives, with your doctor.

Hormone Replacement Therapy (HRT)

HRT use may increase your risk of breast cancer.

HRT is sometimes prescribed to relieve the symptoms of menopause. HRT is not the only option for the management of these symptoms. Other options can be discussed with your doctor.

There are three main types of HRT:

- Combined HRT which contains both oestrogen and progesterone.
- Oestrogen only HRT which is often used in women with no womb.
- Tibolone - a drug that acts like oestrogen in the body.

It is recommended that you use HRT for as short a time as possible and consider other options.

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Screening

Yearly breast screening, such as MRI, may be **recommended** with the addition of mammogram if you are aged 40 or over. If MRI is not available, ultrasound may be offered. Your doctor can discuss the best time to start these tests and which tests to have. You may also wish to attend your doctor for a regular clinical breast examination. Screening aims to detect breast cancer early, before there are any signs or symptoms. Early detection may mean a better chance of successful treatment, but that is not proven for women aged less than 50. Yearly breast screening will not decrease your chance of getting cancer. It is **recommended** that you attend a specialist for a more detailed discussion about screening if you have not already done so.

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Once cancer risks have been estimated, the focus shifts to developing a risk management strategy that considers:

- **Magnitude of the risk**
- **Risks and effectiveness of possible interventions**
- **Individual risk tolerance and preference**

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BRCA1 or BRCA2 – risk management (female)

Lifetime risk of cancer/tumour

Cancer/tumour type	Average risk for BRCA1 pathogenic variant carrier^	Average risk for BRCA2 pathogenic variant carrier	General female population risk**
Breast	72% to age 80 years (95% CI, 65% to 79%)[1]	69% to age 80 years (95% CI, 61% to 77%)[1]	11.9% to age 80 years

Cancer/tumour risk management guidelines

The choice of risk management strategy should take into account current age, other health issues and age-related cancer risk. Risks and benefits of interventions should be discussed with an experienced medical professional.

The impact of lifestyle on cancer risk should be discussed e.g. exercise most days for at least 30 minutes at moderate or strenuous intensity, maintain a healthy weight, have a healthy diet, limit alcohol intake, do not smoke, consider breastfeeding (if relevant), and avoid excessive sun exposure. Decisions about hormonal contraception and menopausal hormone therapy (MHT) should weigh a possible increase in breast cancer risk against the benefits. See Management of associated health issues below for additional information.

Cancer/tumour type	Recommendations		
Breast	**Surgical^**	• Consider bilateral risk-reducing mastectomy • The appropriateness and optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk or iPrevent)	
	Surveillance	• Begin screening from age 25-30 years[6] • Optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk or iPrevent)	
		Age	**Strategy and frequency**
		Under age 40 years	Annual MRI (US if MRI not possible)
		40-60 years	Annual MRI + MMG (MMG + US if MRI not possible)
		Over age 60 years	Annual MMG (consider MRI or US if over age 60 years with dense breast tissue)
		Pregnant	No MRI or MMG, consider US and CBE
	Risk-reducing medication	• Consider medication to reduce risk of developing breast cancer for women not planning bilateral mastectomy within 3 years: ◦ Pre-menopausal women may consider tamoxifen ◦ Post-menopausal women may consider raloxifene, aromatase inhibitors or tamoxifen • See COSA - Medications to lower the risk of breast cancer: clinician guide and offer COSA – Medications to lower the risk of breast cancer: patient guide	

Screening

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Surveillance	• Begin screening from age 25-30 years[b] • Optimal timing should be individualised based on patient preference and risk trajectory (from CanRisk or iPrevent)	
	Age	**Strategy and frequency**
	Under age 40 years	Annual MRI (US if MRI not possible)
	40-60 years	Annual MRI + MMG (MMG + US if MRI not possible)
	Over age 60 years	Annual MMG (consider MRI or US if over age 60 years with der breast tissue)

NSW GOVERNMENT | eviQ

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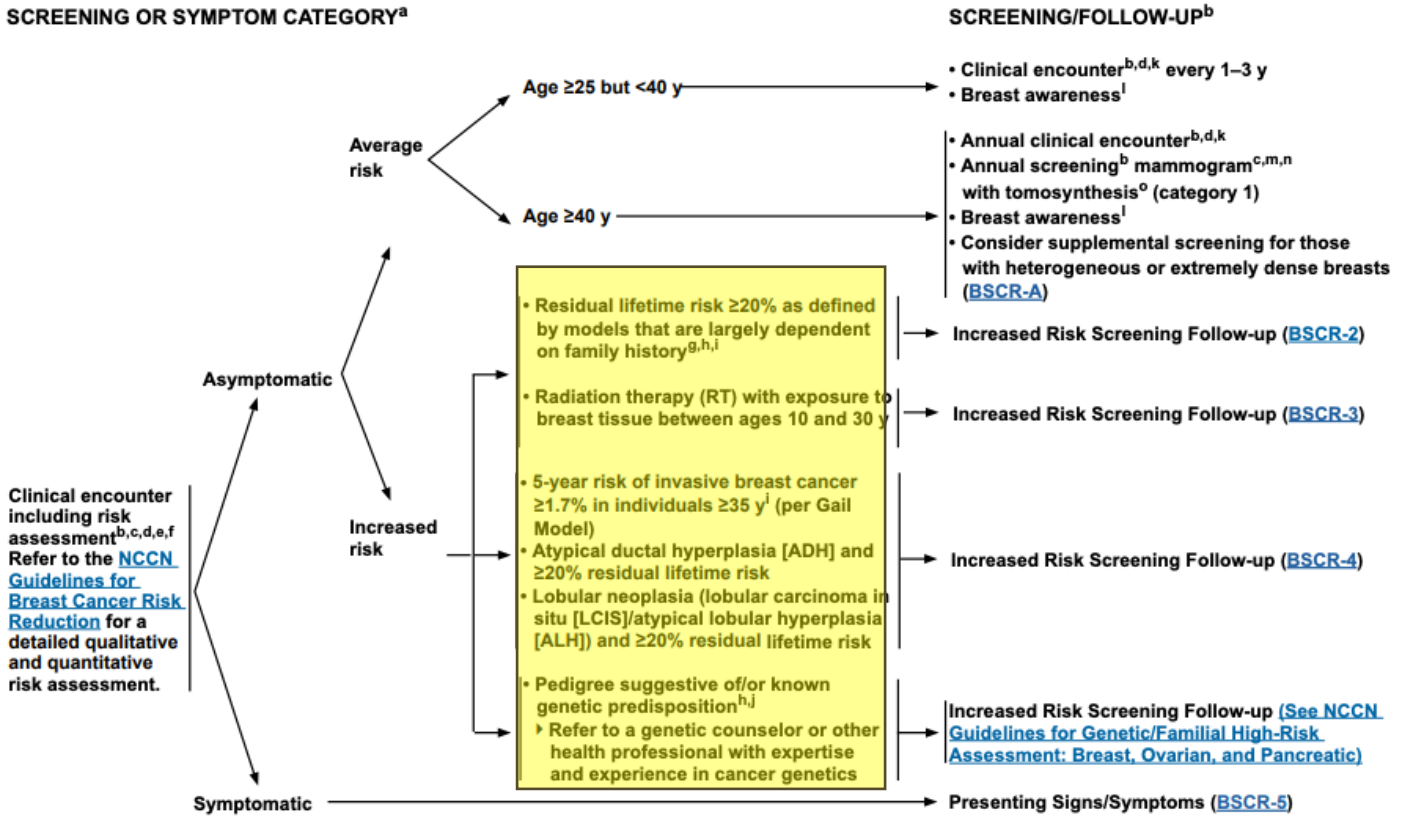
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Breast Cancer Screening and Diagnosis

NCCN Guidelines Index
Table of Contents
Discussion



SCREENING OR SYMPTOM CATEGORY[a]

Increased Risk:

Residual lifetime risk ≥20% as defined by models that are largely dependent on family history[g,h,i]

SCREENING/FOLLOW-UP

- Clinical encounter[b,d,k] every 6–12 mo
  - ‣ To begin when identified as being at increased risk
  - ‣ Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done
  - ‣ Consider referral to a breast specialist as appropriate
- Annual screening[b] mammogram[c,m] with tomosynthesis[o]
  - ‣ To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, or after risk assessment if determined to be at high risk, not prior to age 30 y,[p] or begin at age 40 y (whichever comes first)
- Annual breast MRI[q,r] with and without contrast
  - ‣ Consider contrast-enhanced mammography (CEM)[b] or molecular breast imaging (MBI)[b] for those who qualify for but cannot undergo MRI. Whole breast ultrasound[b] may be done if contrast-enhanced imaging or functional imaging is not available/accessible
  - ‣ To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 y,[s] or after risk assessment if determined to be at high risk, or begin at age 40 y (whichever comes first)
- Consider risk reduction strategies (see NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

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ANNALS OF ONCOLOGY driving innovation in oncology

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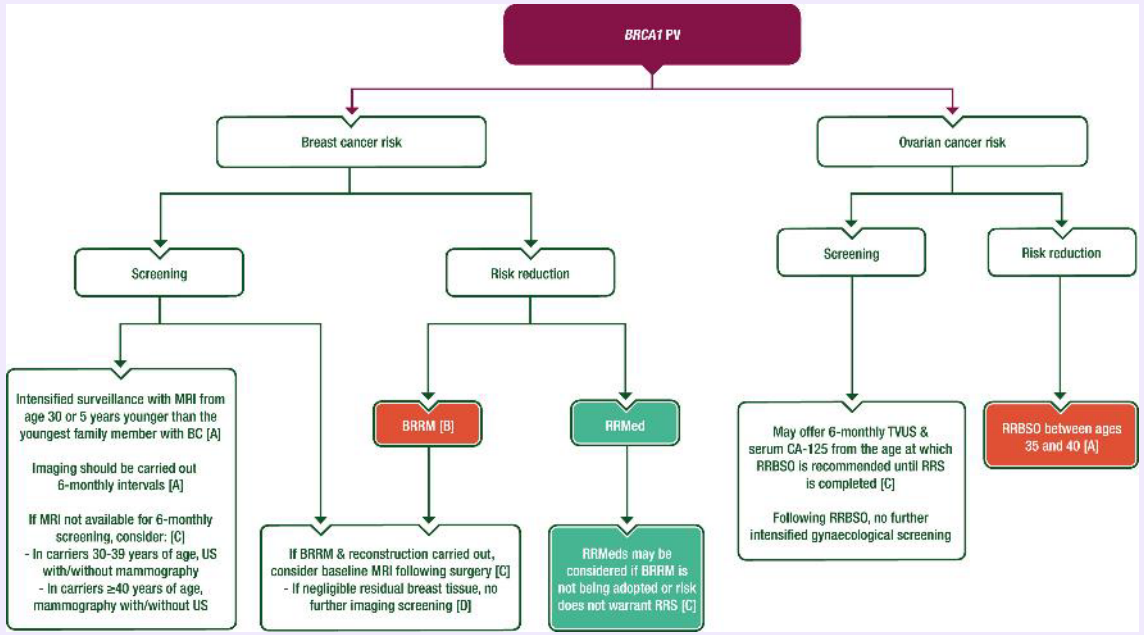
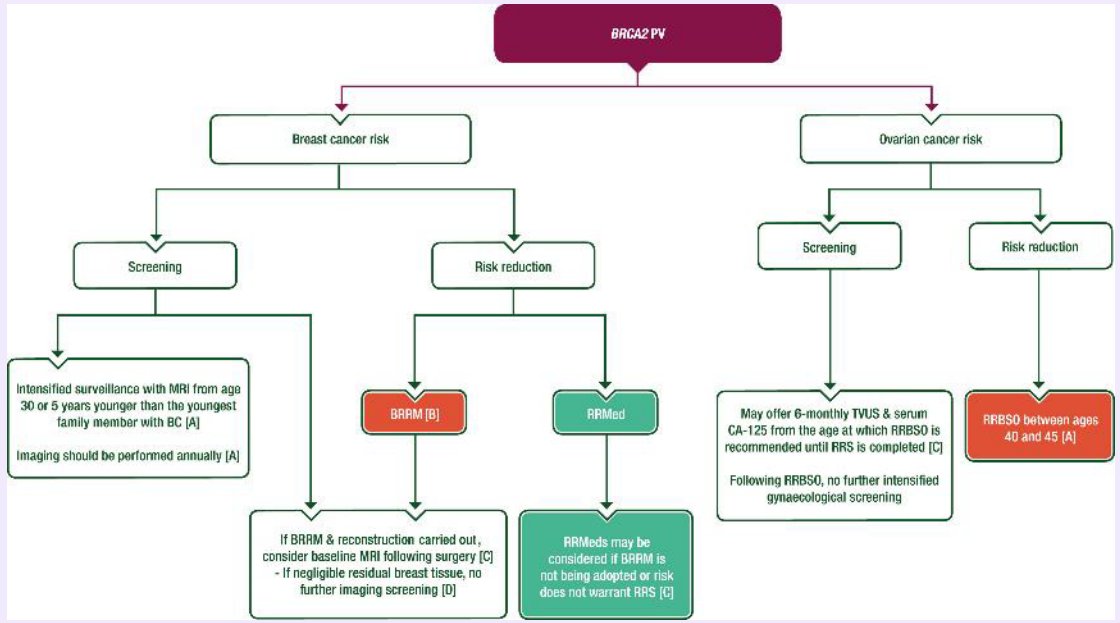
SPECIAL ARTICLE

Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline☆





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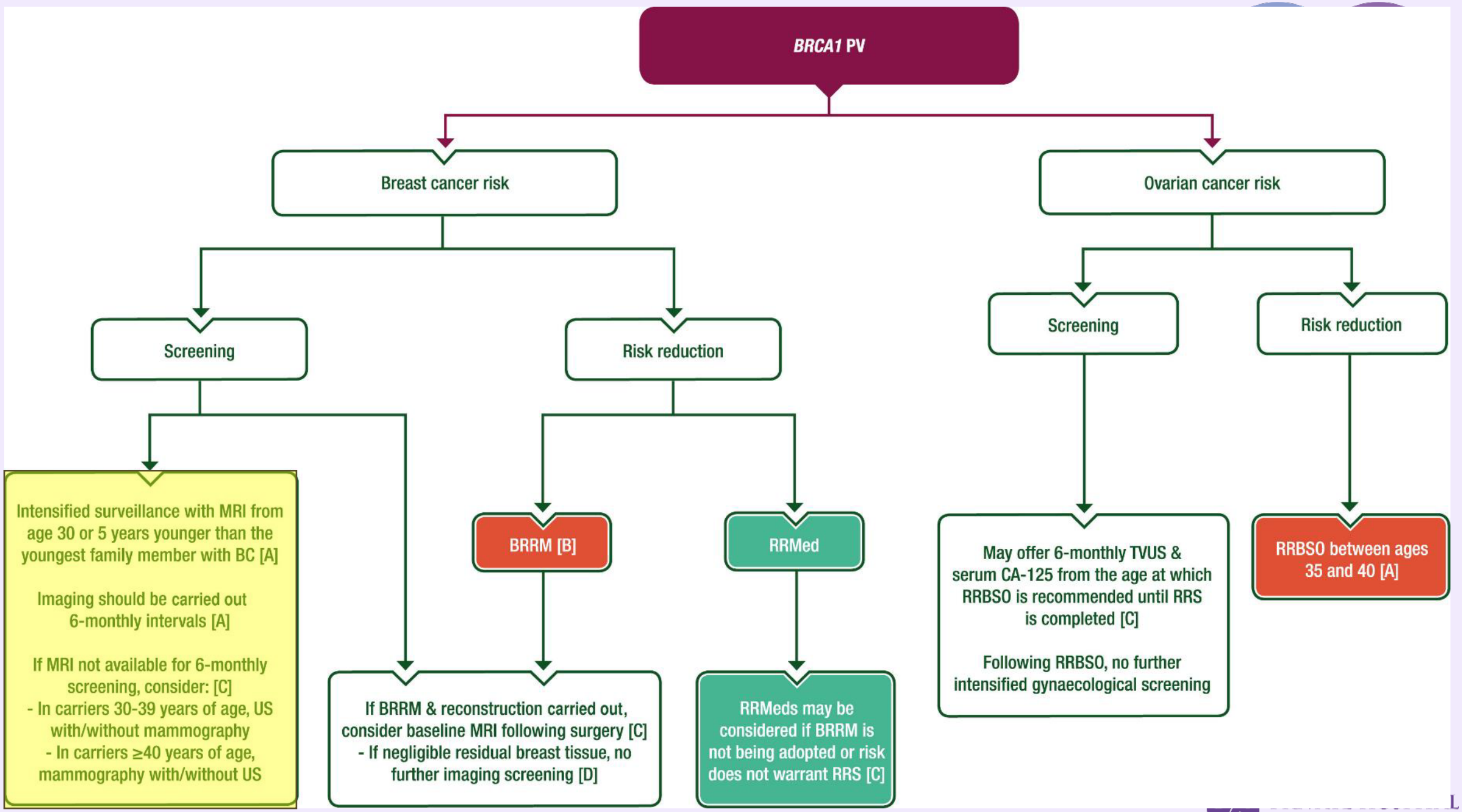
BRCA1 PV
Breast cancer risk
Ovarian cancer risk
Screening
Risk reduction
Screening
Risk reduction
Intensified surveillance with MRI from age 30 or 5 years younger than the youngest family member with BC [A]
Imaging should be carried out 6-monthly intervals [A]
If MRI not available for 6-monthly screening, consider: [C]
- In carriers 30-39 years of age, US with/without mammography
- In carriers ≥40 years of age, mammography with/without US
BRRM [B]
RRMed
If BRRM & reconstruction carried out, consider baseline MRI following surgery [C]
- If negligible residual breast tissue, no further imaging screening [D]
RRMeds may be considered if BRRM is not being adopted or risk does not warrant RRS [C]
May offer 6-monthly TVUS & serum CA-125 from the age at which RRBSO is recommended until RRS is completed [C]
Following RRBSO, no further intensified gynaecological screening
RRBSO between ages 35 and 40 [A]

Medicare High Risk Screening MRI Medicare Eligibility Criteria

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2009

○ MRI SCREENING (eligibility criteria for Medicare rebate below, tick one) ○ MRI NON-REBATABLE (does not meet eligibility criteria)

Asymptomatic female under 50 with:

○ 1. High Risk Br Ca mutation on genetic testing

○ 2. On same side of family

a. 1st or 2nd degree relative with Breast Ca <45 years and another 1st or 2nd degree relative with bone or soft tissue sarcoma <45 years.

b. Three or more 1st or 2nd degree relatives with breast or ovarian Ca.

○ 3. On same side of family, two 1st or 2nd degree relatives with breast or ovarian Ca and one relative with one of the following:

a. Bilateral breast Ca
b. Onset Breast Ca before age 40
c. Onset Ovarian Ca before age 50
d. Breast and ovarian Ca in one relative
e. Breast Ca in a male relative
f. Ashkenazi Jewish ancestry

Nov 2022

○ MRI SCREENING (eligibility criteria for Medicare rebate below, tick one) ○ MRI NON-REBATABLE (does not meet eligibility criteria)

Asymptomatic female under 60 years of age; and
the request for the scan identifies that the patient is at high risk of developing breast cancer due to one or more of the following:

○ (i) genetic testing has identified the presence of a high risk breast cancer gene mutation in the patient or in a first degree relative of the patient;

○ (ii) both:

(A) one of the patient's first or second degree relatives was diagnosed with breast cancer at age 45 years or younger; and

(B) another first or second degree relative on the same side of the patient's family was diagnosed with bone or soft tissue sarcoma at age 45 years or younger;

○ (iii) the patient has a personal history of breast cancer before the age of 50 years;

○ (iv) the patient has a personal history of mantle radiation therapy;

○ (v) the patient has a lifetime risk estimation greater than 30% or a 10 year absolute risk estimation greater than 5% using a clinically relevant risk evaluation algorithm.

Applicable not more than once in a 12 month period.

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JAMA Insights | WOMEN'S HEALTH

Risk-Reducing Mastectomy

Ismail Jatoi, MD, PhD; Zoe Kemp, MD, PhD

Risk-reducing mastectomy (RRM) refers to surgical removal of the breasts in the absence of malignancy to reduce breast cancer risk in women (**Table**).[1] RRM is synonymous with *prophylactic mastectomy*, and is further specified as either bilateral or contralateral. Bilateral RRM (BRRM) refers to removal of both breasts in asymptomatic women, while contralateral RRM (CRRM) refers to removal of the unaffected breast when bilateral mastectomy is performed for the management of unilateral breast cancer.[1] In high-risk patients, RRM is associated with reduction in breast cancer risk and potential adverse effects on quality of life.[1] Thus, prior to any RRM procedure, patients should be informed of the potential for both benefit and harm.

JAMA Patient Page page 1804

Indications for Risk-Reducing Mastectomy

Rare high-risk germline pathogenic variants (ie, mutations) in women are associated with increased breast cancer risk, with lifetime risk exceeding 50% for women with these variants vs 12% for those without.[2] Asymptomatic carriers of these variants may wish to consider BRRM, and carriers diagnosed with unilateral breast cancer may

drome), *PTEN* (phosphatase and tensin homologue; Cowden syndrome), *STK11* (Peutz-Jeghers syndrome), *CDH1* (hereditary diffuse gastric cancer syndrome), and *PALB2* genes.[2,4] For *STK11*, *CDH1*, and *PALB2* variant carriers, RRM should be considered on the basis of family history.[4]

Besides BRRM, high-risk variant carriers should be informed of 2 other risk-reducing options: screening (with mammography and breast magnetic resonance imaging) and chemoprevention (ie, medications administered for 5 years).[4] For asymptomatic carriers of moderate-risk variants (including pathogenic variants in the *ATM* and *CHECK2* genes, associated with lifetime breast cancer risk ranging between 25% and 50%), BRRM is generally not indicated, and screening and chemoprevention are preferred options for risk reduction.[4] Additionally, CRRM is generally not indicated for carriers of moderate-risk variants with unilateral breast cancer.[4,5]

Genetic testing often identifies variants with uncertain pathogenicity, referred to as *variants of unknown/uncertain significance*.[2] A variant of unknown significance should not influence surgical decision-making and is not an indication for RRM.

RRM may also be considered for women treated before age 30 years with chest wall irradiation for Hodgkin lymphoma or other

Risk-Reducing Medication

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RISK-REDUCING MEDICATIONS

- Level 1 efficacy in primary prevention of oestrogen positive BC[1-7]
- Daily tablet taken for 3 to 5 years
- Relative **risk reduction between 30% to 60%**
- Risk reduction continues long after medications ceased[5-7]
- 4 evidence-based risk reducing medications

  Selective Oestrogen Receptor Modulators
  - ❖Tamoxifen (pre-menopausal and post-menopausal)
  - ❖ Raloxifene (post-menopausal)

  Aromatase Inhibitors
  - ❖Anastrozole (post-menopausal)
  - ❖Exemestane (post-menopausal)
- Endorsed by national and international guidelines[8-11]

Peter Mac

1. **IBIS I** Cuzick et al. *Lancet* (2002); 2. **IBIS II** Cuzick et al. *Lancet* (2014); 3. NCIC CTG **MAP.3 trial** Richardson et al. *Curr Oncol* (2007); 4. **STAR** trial - Vogel et al. *JAMA* (2006), 5. Low-Dose Tam trial -. Lazzeroni et al. *J clin Oncol* (2023); 6. **IBIS I update** Cuzick et al. *Lancet Oncol* (2015); 7.**IBIS II update**– Cuzick et al. *the Lancet* (2020).
8. Visanathan et al. ASCO. *J clin Onc* (2009); 9. NCCN Clinical Practice Guidelines (2024); 10. NICE. Clinical Guideline 2023; 11. Cancer Institute NSW evIQ 2021.

Slide courtesy Kelly Phillips

Medications to lower the risk of breast cancer

CLINICIAN GUIDE

Clinical Oncology Society of Australia

www.cosa.org.au

NICE National Institute for Health and Care Excellence

Patient decision aid

Taking tamoxifen to reduce the chance of developing breast cancer

Decision aid for premenopausal women at high risk

www.nice.org.uk

Risk-Reducing Intervention	%
RRM	21
RRBSO	38
RRM and RRBSO	12
Risk Reducing Medication (on trial)	3
Risk Reducing Medication (off trial)	<1

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PREVENTING CANCER WITH MEDICATIONS (PCMED)

TELEHEALTH SERVICE

Katrina West RN, Grad Dip(Cancer Nursing), MN (NPract)
Nurse Practitioner
PCMed Co-Lead, Peter MacCallum Cancer Centre
MPhil Candidate, University of Melbourne

Preventing Cancer with Medications Telehealth Service

Did you know a tablet taken daily for 3-5 years, can reduce your risk of breast cancer by 30-60% and the benefits can last for many years after stopping?

The Preventing Cancer with Medications Telehealth Service supports women to understand their risk of breast cancer and decide whether to use a daily tablet to help prevent breast cancer.

Who is suitable?

- Female.
- Aged between 20 and 70 years.
- At **increased risk** of breast cancer.
- Want to consider whether to take a daily tablet to reduce breast cancer risk.
- No previous breast cancer or ductal carcinoma in situ (DCIS).

You will be asked to complete a health questionnaire and an online assessment of your breast cancer risk to assess your suitability for the Service.

What is involved?

- You will be invited to attend 1-2 telehealth appointments to discuss breast cancer prevention medications.
- For those who decide to start a medication, there is a follow-up appointment 8-10 weeks later.
- Your referring doctor and GP will be sent information.
- There is no cost for women to attend the Service.

This service is delivered via Telehealth

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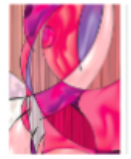
WHY DO WE NEED THE SERVICE?

Underutilisation of breast cancer prevention medication in Australia

Courtney Macdonald [a, b], James A. Chamberlain [c], Danielle Mazza [d], Roger L. Milne [c, e, f], kConFab investigators [b, g], Kelly-Anne Phillips [a, b, e, *]

[a] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[b] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[c] Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia
[d] Department of General Practice, Monash University, Melbourne, Australia
[e] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia
[f] Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Melbourne, Australia
[g] The Research Department, Peter MacCallum Cancer Centre, Melbourne, Australia



- Despite evidence & guidelines, use is low
- Only 2.4% of Australian women who know they are at increased risk have ever taken them

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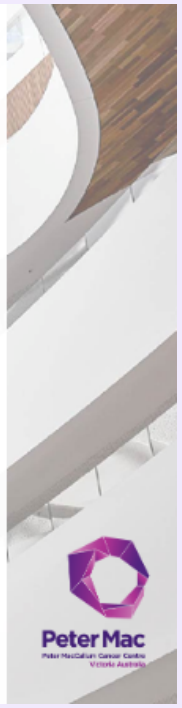
Victoria Australia

WHO IS SUITABLE?

- Female.
- Aged 20 to 70 years.
- No invasive BC or DCIS.
- Increased BC risk
  - Remaining lifetime BC risk ≥ 20% or 10-year risk of ≥ 5%, or
  - LCIS or AH, or
  - Previous chest irradiation < age 35 (> 5 years prior).
- No bilateral mastectomy or use of RRMeds.
- No major BC predisposition gene mutation, or 1st degree relative of a carrier (unless referred by Risk Management Clinic).
- Do not need genetic testing to clarify risk.



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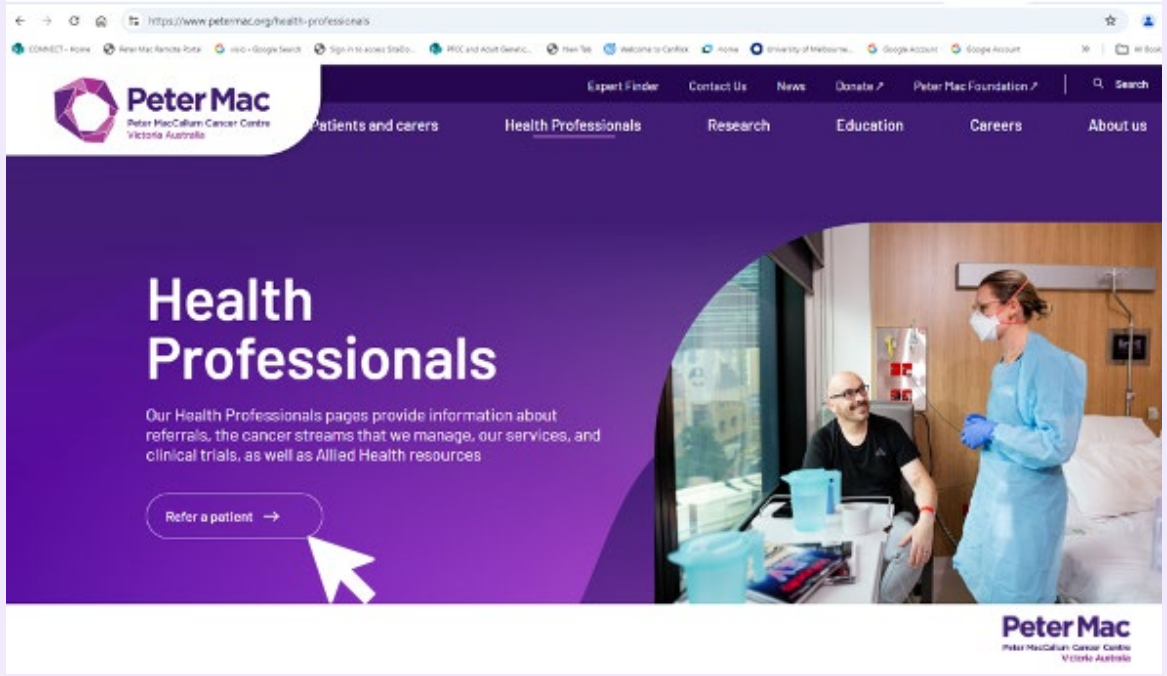
REFERRAL TO PCMED SERVICE



Referrals: PCMedService@petermac.org

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Decision Making

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> Don't ever make decisions based on fear. Make decisions based on hope and possibility. Make decisions based on what should happen, not what shouldn't.

"The longer people need to make a choice, the less confident they are with their decision.

'It's difficult to make the right choice if you fear choosing wrongly.'

I am empowered to take control of my life and shape my own destiny

HOPE IS NOT A STRATEGY

When you have to make a choice and don't make it, that is in itself a choice.

UNCERTAINTY WILL ALWAYS BE PART OF THE TAKING CHARGE PROCESS

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RISK-REDUCING SURGERY

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- Why ?
- For Whom ?
- If ?
- When ?
- What ?
- Where ?

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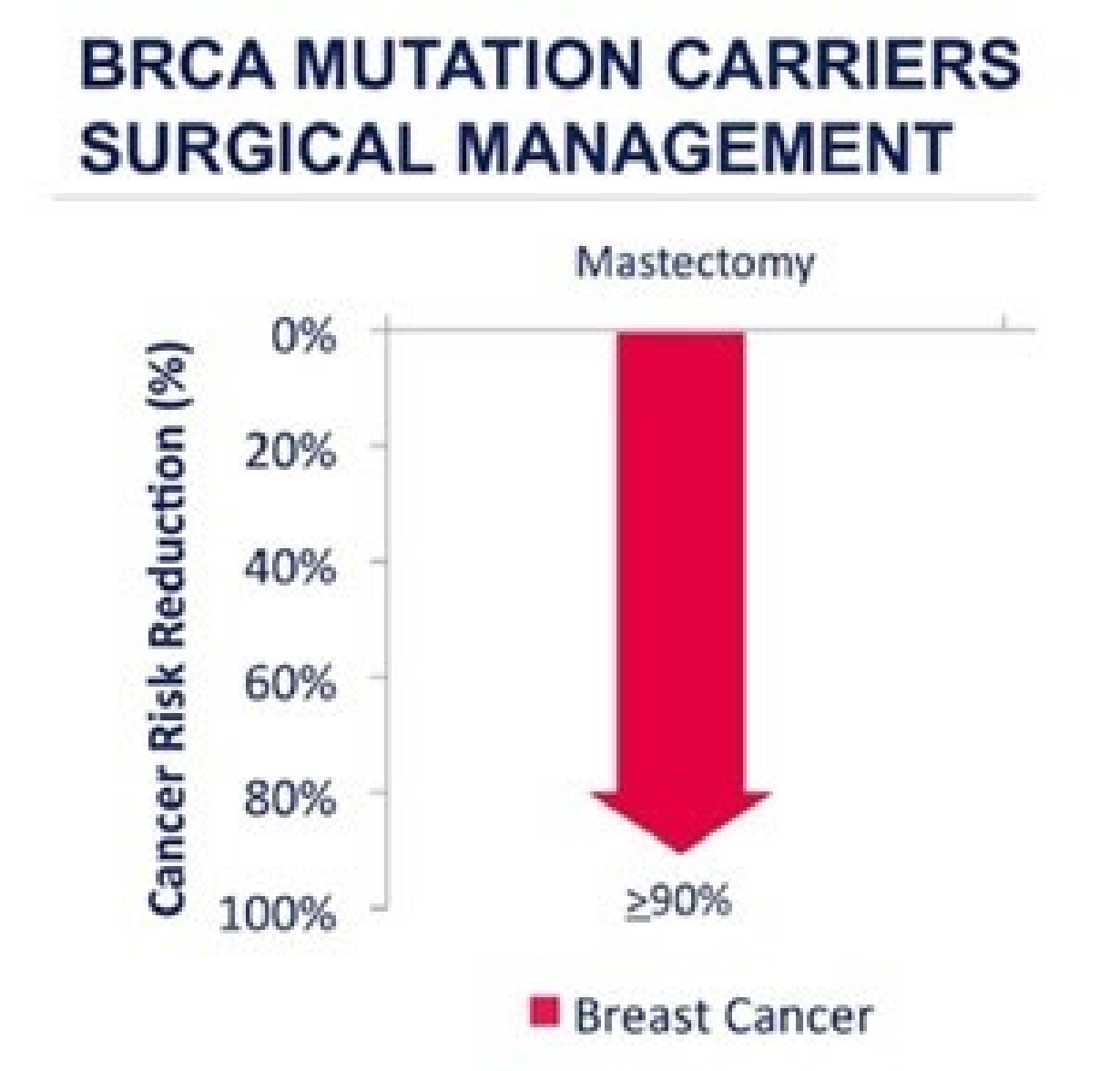
WHY ?



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Risk-Reducing Mastectomy

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Society of Surgical Oncology Breast Disease Working Group Statement on Prophylactic (Risk-Reducing) Mastectomy

Kelly K. Hunt, MD[1], David M. Euhus, MD[2], Judy C. Boughey, MD[3], Anees B. Chagpar, MD[4], Sheldon M. Feldman, MD[5], Nora M. Hansen, MD[6], Swati A. Kulkarni, MD[6], David R. McCready, MD[7], Eleftherios P. Mamounas, MD[8], Lee G. Wilke, MD[9], Kimberly J. Van Zee, MD[10], and Monica Morrow, MD[10]

[1]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Johns Hopkins University, Baltimore, MD; [3]Mayo Clinic, Rochester, MN; [4]Yale University, New Haven, CT; [5]Columbia University, New York, NY; [6]Northwestern University, Chicago, IL; [7]University of Toronto, Toronto, ON, Canada; [8]Orlando Health, Orlando, FL; [9]University of Wisconsin, Madison, WI; [10]Memorial Sloan Kettering Cancer Center, New York, NY

Ann Surg Oncol (2017) 24:375–397

- From the published data it is clear that BRRM confers a reduction in the risk of developing a primary breast cancer approaching **100%** when meticulous surgical technique is used to remove the vast majority of breast tissue.
- The breast cancer risk reduction from BRRM is greatest in healthy, unaffected women with a known genetic predisposition
- Almost all new breast cancers after BPM occur in patients who had significant breast tissue remaining, such as those who ho had residual breast tissue in the axillary tail after surgery

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FOR WHOM?

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Lifetime *BRCA1* and *BRCA2* Cancer Risks for Women

TYPE OF CANCER	Woman with *BRCA1* Mutation	Woman with *BRCA2* mutation	Average woman in US without mutation
Breast	60–80%	50–70%	13%
Ovarian	30–45%	10–20%	1–2%
Pancreatic	2–3%	3–5%	1%
Melanoma	–	3–5%	1–2%
Uterine	1	–	2–3%

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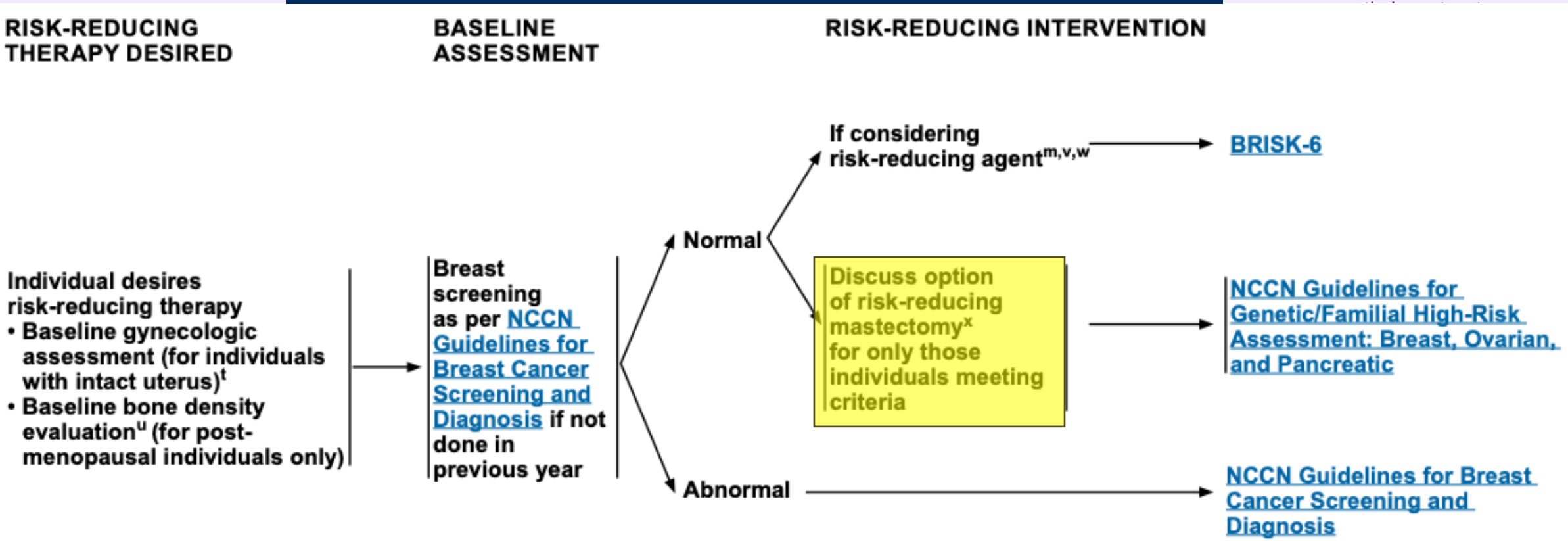

[x] Risk-reducing mastectomy should generally be considered in individuals with a pathogenic/likely pathogenic genetic variant in high-penetrance breast cancer susceptibility genes (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic), compelling family history, or those receiving chest wall radiation before 30 years of age. There is no established benefit of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants in moderate- or low-penetrance breast cancer susceptibility genes in the absence of a compelling family history. While this approach has been previously considered for LCIS, the currently preferred approach for LCIS is a risk-reducing endocrine agent. Risk estimation is a complex and individualized process; the NCCN Panel does not recommend a specific risk cutoff for decision-making regarding risk-reducing mastectomy. Individualizing management is important.

- BRCA or other high-risk mutation
- Prior thoracic radiation therapy delivered at age younger than 30-35 yrs
- Histological risk factors (eg LCIS)
- Contralateral Prophylactic Mastectomy(CPM) in patients with Unilateral Breast Cancer
- "Compelling" family history

RRM is currently "offered" rather than "recommended"

Women opt for surgery of their own volition

There is no single risk threshold above which RRM is clearly indicated, however unlikely to be considered for risk below 30%

Risk-Reducing Surgery should NOT be undertaken under the following circumstances:

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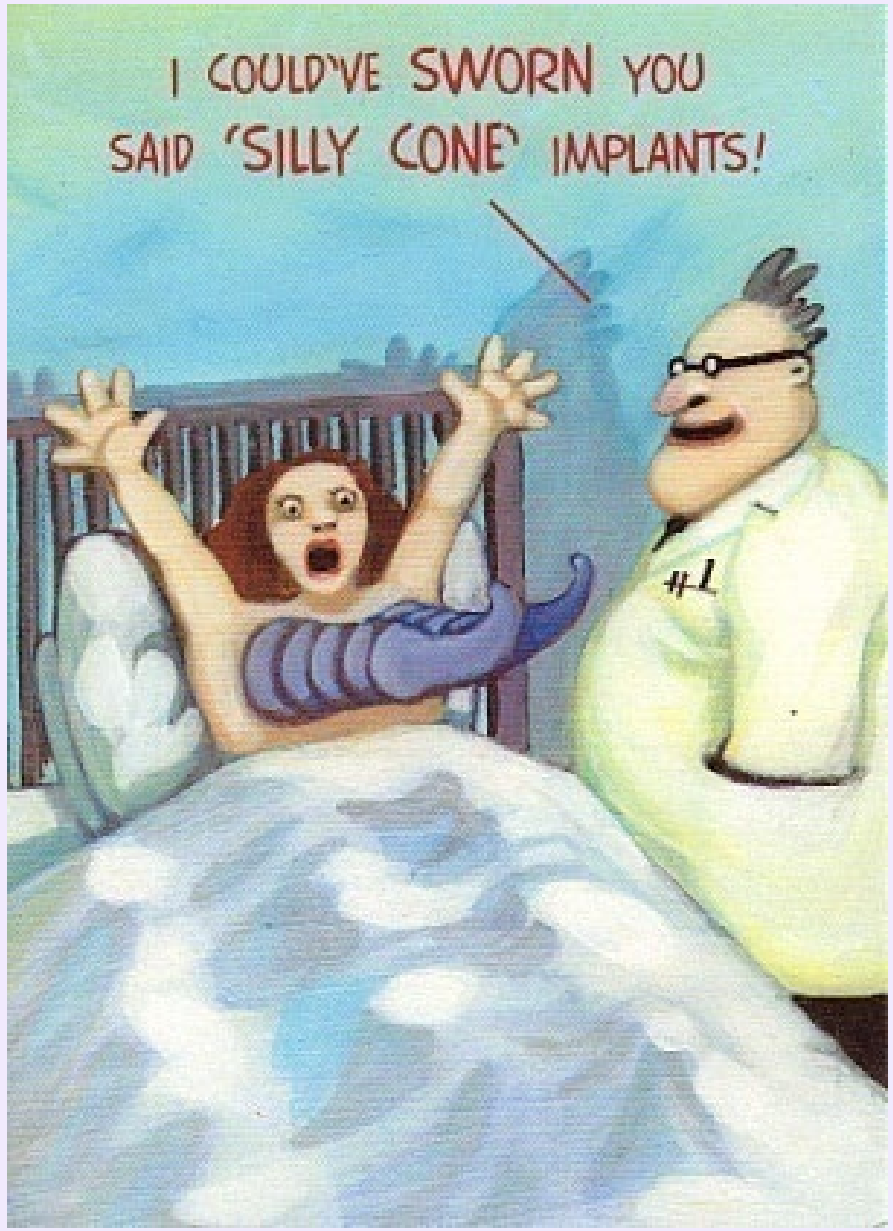
- Individual risk cannot be substantiated
- Factitious family history
- Munchausen's syndrome
- Gene test result imminent
- Surgery is not the woman's own choice
- Choice of surgery is for cosmetic rather than oncological reasons
- Psychiatric disorder, clinical depression, cancer phobia, dysmorphic syndrome
- Co-morbidity outweighs potential clinical benefit
- Immoveable unrealistic expectation of outcome



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Expectations need to be be realistic and achievable

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IF ?

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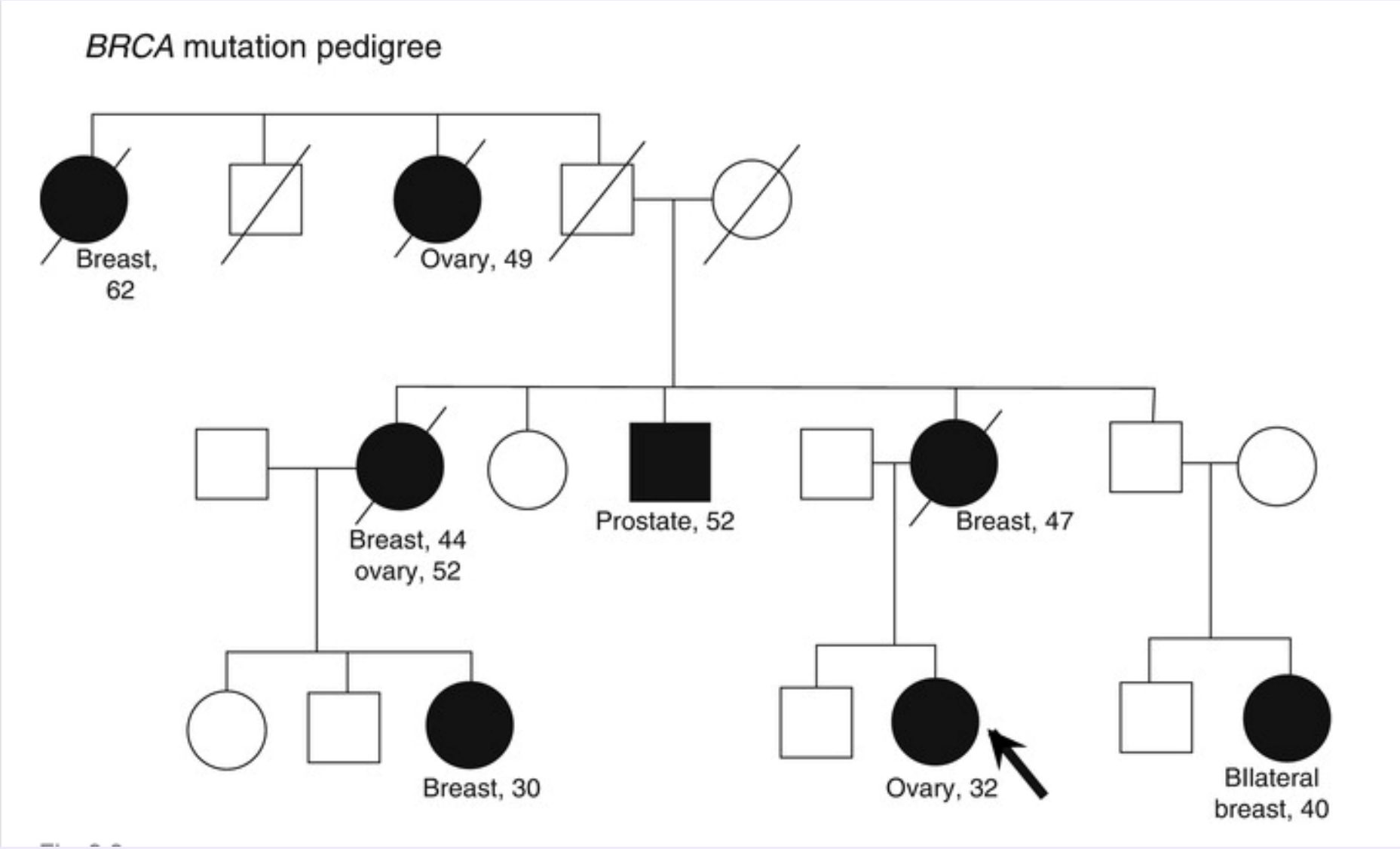
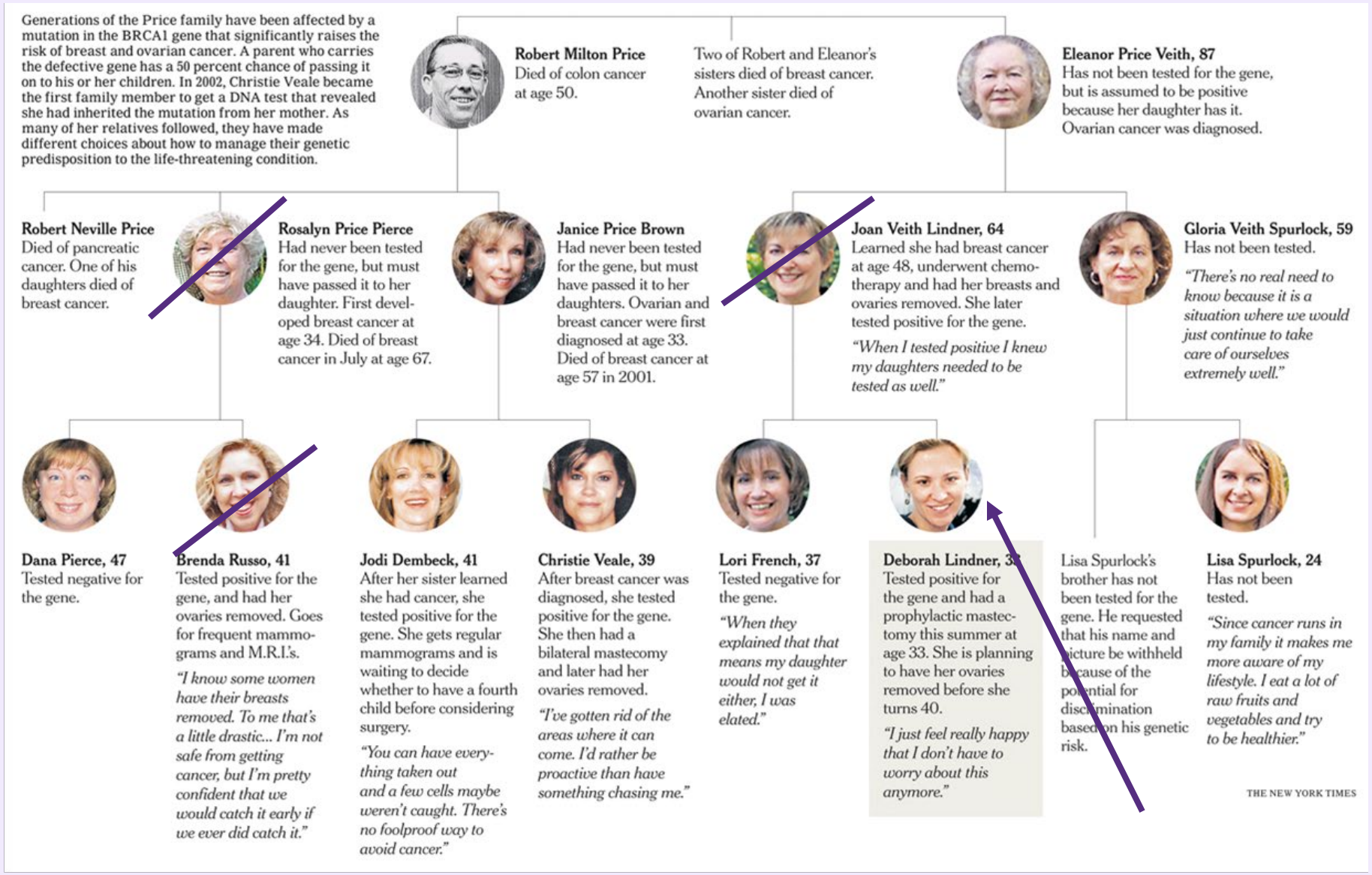
Pedigree- what we see



Pedigree- what the patient sees



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Risk-Reducing Mastectomy Uptake Rates

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International variation in rates of uptake of preventive options in *BRCA1* and *BRCA2* mutation carriers

Kelly A. Metcalfe[1,2], Daphna Birenbaum-Carmeli[3], Jan Lubinski[4], Jacek Gronwald[4], Henry Lynch[5], Pal Moller[6], Parviz Ghadirian[7], William D. Foulkes[8,9,10], Jan Klijn[11], Eitan Friedman[12,13], Charmaine Kim-Sing[14], Peter Ainsworth[15], Barry Rosen[16], Susan Domchek[17,18], Teresa Wagner[19], Nadine Tung[20], Siranoush Manoukian[21], Fergus Couch[22], Ping Sun[2], Steven A. Narod[2*] and the Hereditary Breast Cancer Clinical Study Group

Austria	Canada	France	Israel	Italy	Holland	Norway	Poland	USA
20%	22.4%	25%	4.2%	10%	32.7%	4.5%	2.7%	36.3%

Int J Cancer 2008

- Enormous variation worldwide 3-36%
- >50% of women rely on screening alone
- 20-30% do not have recommended regular screening tests

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Preventing breast and ovarian cancers in high-risk *BRCA1* and *BRCA2* mutation carriers

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3 Uptake of risk-reducing interventions among 325 women who were aware that they carried a ***BRCA1*** or ***BRCA2*** mutation

Risk-reducing intervention	Number	Age at intervention (years)	
		Median	Range
RRM*	69 (21%)	40	26–67
RRBSO†	125 (38%)	44	30–77
By age 40‡	16/62		
BRCA1	12/35		
BRCA2	4/27		
By age 50§	29/44		
BRCA1	17/27		
BRCA2	12/17		
Both RRM and RRBSO	38 (12%)	—	—
Risk-reducing medication or placebo (on trial)	9 (3%)	36	35–56
Risk-reducing medication (off trial)	1 (< 1%)	—	—
Tubal ligation¶	71 (22%)	32	20–54

RRBSO = risk-reducing bilateral salpingo-oophorectomy. RRM = risk-reducing mastectomy.
* Seven before cohort entry. † Eight before cohort entry. ‡ Restricted to 62 women who were followed to at least the age of 40 years and knew their genetic result before the age of 40 years. § Restricted to 44 women who were followed to at least the age of 50 years and knew their genetic result before the age of 50 years. ¶ 60 before cohort entry. ◆

MJA May 2013

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Table 3: Uptake of risk-reducing interventions among 325 women who were aware they carried a *BRCA1* or *BRCA2* mutation

		Age at intervention (yrs)	
Risk-reducing intervention	**Number**	**Median**	**Range**
RRM (Risk-reducing mastectomy)	69/325 (21%) Seven before cohort entry	40	26–67
RRBSO (Risk-reducing bilateral salpingo-oophorectomy)	125/325 (38%) Eight before cohort entry	44	30–77
By age 40 *Restricted to 62 women who were followed to at least the age of 40 years and knew their genetic result before the age of 40 years*	16/62		
BRCA1	12/35		
BRCA2	4/27		
By age 50 Restricted to 44 women who were followed to at least the age of 50 years and knew their genetic result before the age of 50 years	29/44		
BRCA1	17/27		
BRCA2	12/17		
Both RRM and RRBSO	38/325 (12%)	–	–
Risk-reducing medication or placebo (on trial)	9/325 (3%)	36	35–56
Risk-reducing medication (off trial)	1/325 (< 1%)	–	–
Tubal ligation	71/325 (22%) 60 before cohort entry	32	20–54

Collins IM, et al. Preventing breast and ovarian cancers in high-risk BRCA1 and BRCA2 mutation carriers. *Medical Journal of Australia* 2013; 199(10):680-83.

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Risk-Reducing Intervention	%
RRM	21
RRBSO	38
RRM and RRBSO	12
Risk Reducing Medication (on trial)	3
Risk Reducing Medication (off trial)	<1

MJA May 2013

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Original article

Psychological factors associated with the intention to choose for risk-reducing mastectomy in family cancer clinic attendees

C.M.G. van Driel [a, *], J.C. Oosterwijk [b], E.J. Meijers-Heijboer [c], C.J. van Asperen [d], I.A. Zeijlmans van Emmichoven [e], J. de Vries [f], M.J.E. Mourits [a], L. Henneman [c, g], D.R.M. Timmermans [g, h], G.H. de Bock [i]

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Risk-reducing mastectomy in *BRCA1/2* mutation carriers: Factors influencing uptake and timing

Catheleine M. van Driel [a,*], Yassir Eltahir [b], Jakob de Vries [c], Jan P. Jaspers [d], Jan C. Oosterwijk [e], Marian J. Mourits [f], Geertruida H. de Bock [a]

[a] Departments of Epidemiology, University Medical Center, University of Groningen, Groningen, The Netherlands
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[c] Surgery, University Medical Center, University of Groningen, Groningen, The Netherlands
[d] Medical Psychology, University Medical Center, University of Groningen, Groningen, The Netherlands
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[f] Gynaecology, University Medical Center, University of Groningen, Groningen, The Netherlands

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What influences uptake of RRM?

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- Risk perception
- Anxiety
- Family history
- Patient knowledge
- Patient demographic and socioeconomic factors
- Health care professionals' recommendation
- Access to care (cost and availability)
- Mutation type influence on uptake of RRBSO

Metcalfe, K, et al. Int. J. Cancer (2008)
Meiser et al J Womens Health (Larchmt). 2003
Madalinska et al J Clin Oncol. 2007
Metlcalfe et al J Clin Oncol. 2008

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- Decisions regarding preventive surgery are influenced by much more than the actual risk figure
- Individual life experience, and in particular the loss of a mother significantly impacts decision making, regardless of age or risk
- Shared decision-making leads to higher levels of patient satisfaction, but physicians struggle to gauge patient preference for paternalism vs. autonomy
- While some women feel disappointed that a physician was not more directive, others reject doctors' input as too forceful or definitive

- An important predictor of a patient later regretting having had RRM is when the physician was the one to introduce this option into the discussion of treatment

- This emphasizes that physicians must be well aware of how much they may influence a woman's decision to have prophylactic surgery, and they must remain alert when giving advice about possible treatment and monitoring options and verify whether the choice for prophylactic surgery is based on the patients' own decision.

Incidence of regret low (6%)

More common in women:

- Dissatisfied with cosmetic result
- Those who felt misinformed about their options preoperatively

WHEN ?

Timing

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- Determining the optimal timing of risk-reducing mastectomy requires an understanding of both lifetime risk and near-term risk.

Mean age at diagnosis of breast cancer:

- 44 years for BRCA1
- 47 years for BRCA2

- Age at onset varies by family, particularly for families with BRCA2 mutations.

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Research

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

JAMA June 20, 2017 Volume 317, Number 23

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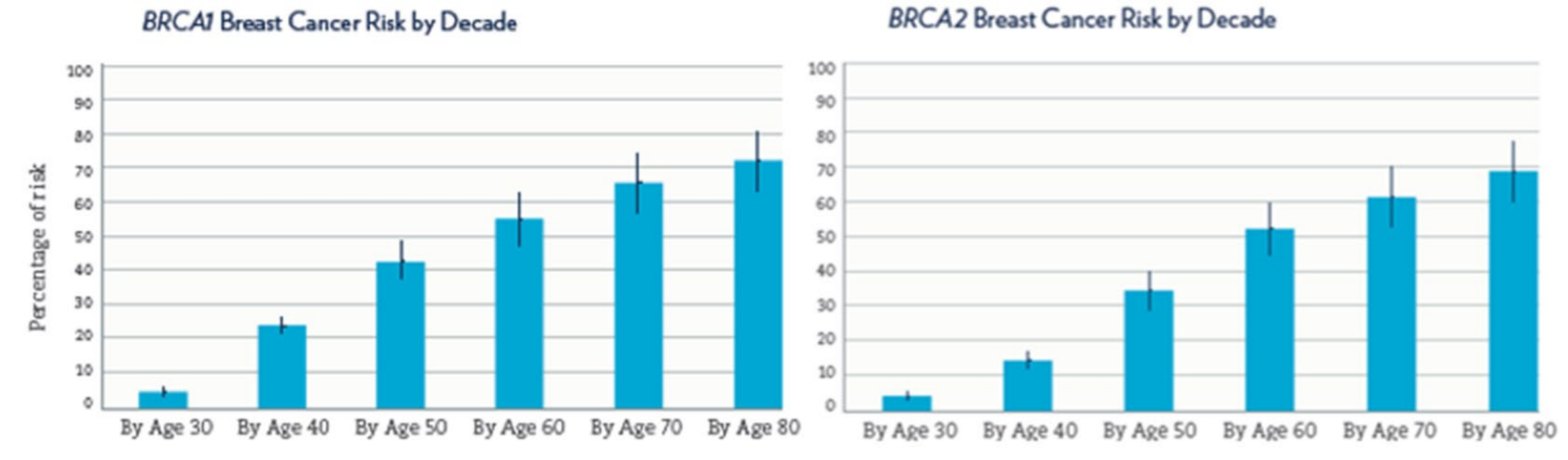

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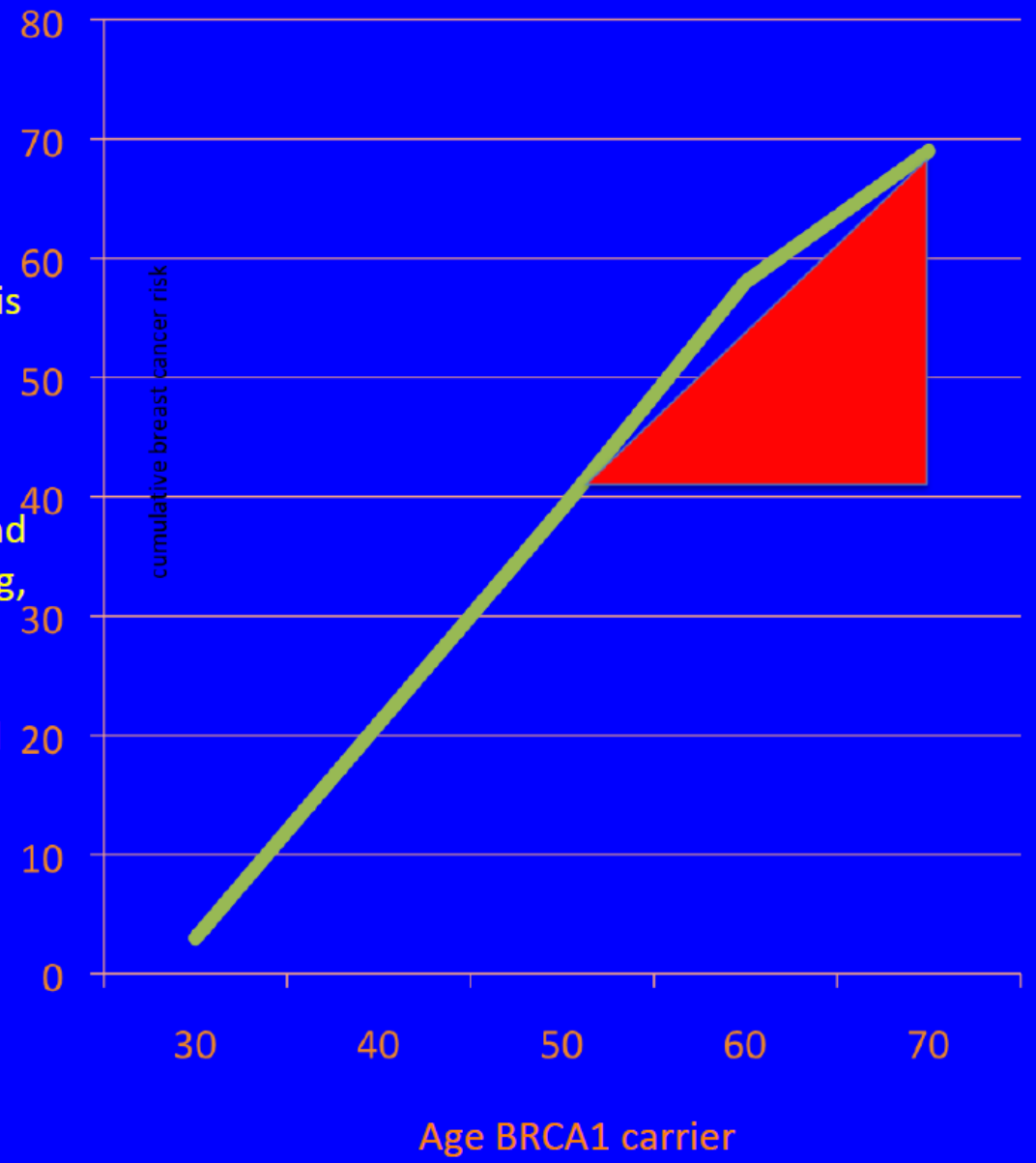
Area Under the Curve Concept of Future Risk

For a 30 year old woman just found to be a BRCA 1 carrier the entire lifetime risk curve is applied

For a 50 year old who has no personal history of cancer, and completed negative screening, her risk is estimated as the area under the curve of remaining risk a 30% residual risk



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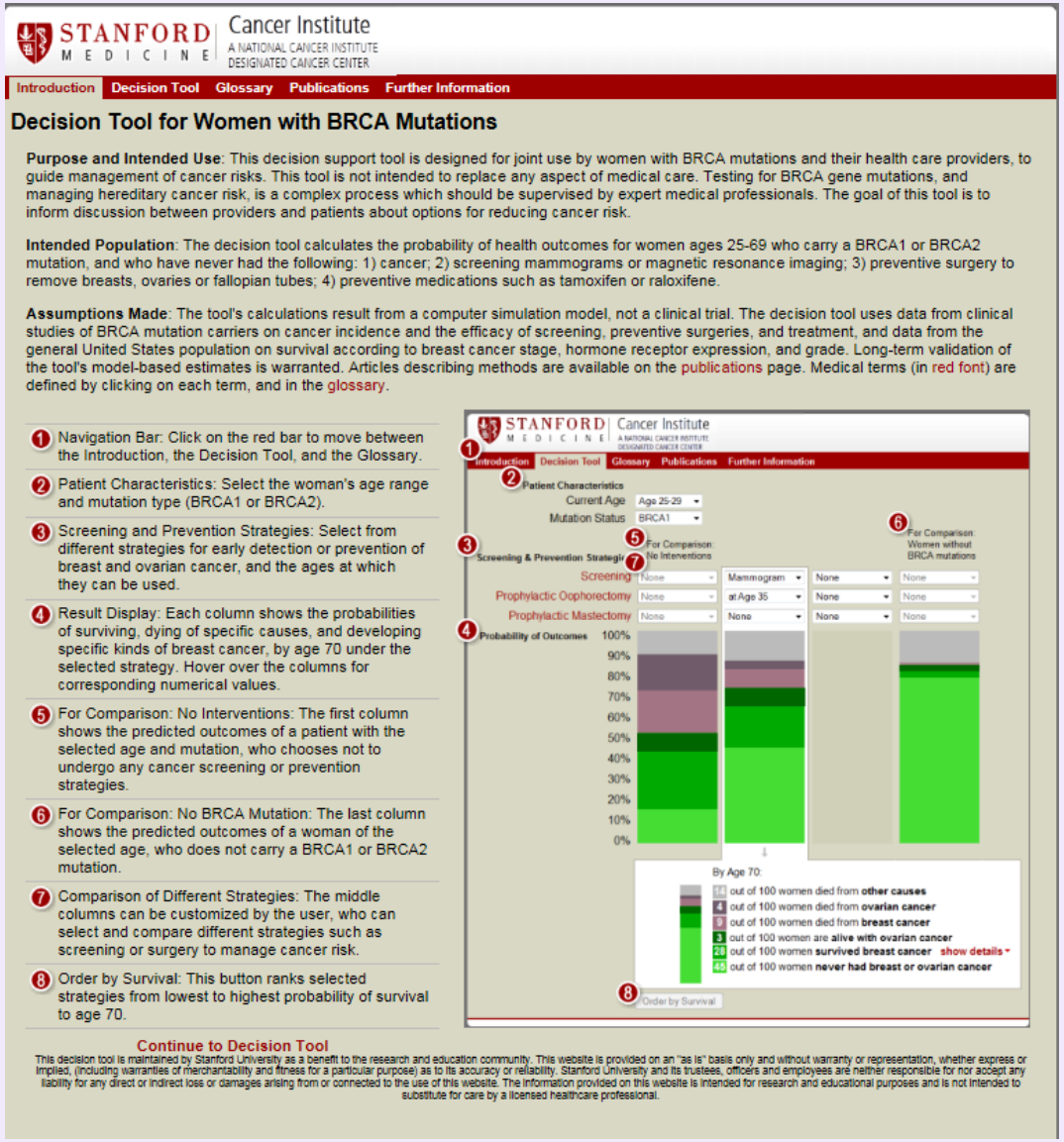
Online Decision Tool



STANFORD MEDICINE | Cancer Institute
A NATIONAL CANCER INSTITUTE DESIGNATED CANCER CENTER

Introduction | Decision Tool | Glossary | Publications | Further Information

Decision Tool for Women with BRCA Mutations

Purpose and Intended Use: This decision support tool is designed for joint use by women with BRCA mutations and their health care providers, to guide management of cancer risks. This tool is not intended to replace any aspect of medical care. Testing for BRCA gene mutations, and managing hereditary cancer risk, is a complex process which should be supervised by expert medical professionals. The goal of this tool is to inform discussion between providers and patients about options for reducing cancer risk.

Intended Population: The decision tool calculates the probability of health outcomes for women ages 25-69 who carry a BRCA1 or BRCA2 mutation, and who have never had the following: 1) cancer; 2) screening mammograms or magnetic resonance imaging; 3) preventive surgery to remove breasts, ovaries or fallopian tubes; 4) preventive medications such as tamoxifen or raloxifene.

Assumptions Made: The tool's calculations result from a computer simulation model, not a clinical trial. The decision tool uses data from clinical studies of BRCA mutation carriers on cancer incidence and the efficacy of screening, preventive surgeries, and treatment, and data from the general United States population on survival according to breast cancer stage, hormone receptor expression, and grade. Long-term validation of the tool's model-based estimates is warranted. Articles describing methods are available on the publications page. Medical terms (in red font) are defined by clicking on each term, and in the glossary.

1. Navigation Bar: Click on the red bar to move between the Introduction, the Decision Tool, and the Glossary.
2. Patient Characteristics: Select the woman's age range and mutation type (BRCA1 or BRCA2).
3. Screening and Prevention Strategies: Select from different strategies for early detection or prevention of breast and ovarian cancer, and the ages at which they can be used.
4. Result Display: Each column shows the probabilities of surviving, dying of specific causes, and developing specific kinds of breast cancer, by age 70 under the selected strategy. Hover over the columns for corresponding numerical values.
5. For Comparison: No Interventions: The first column shows the predicted outcomes of a patient with the selected age and mutation, who chooses not to undergo any cancer screening or prevention strategies.
6. For Comparison: No BRCA Mutation: The last column shows the predicted outcomes of a woman of the selected age, who does not carry a BRCA1 or BRCA2 mutation.
7. Comparison of Different Strategies: The middle columns can be customized by the user, who can select and compare different strategies such as screening or surgery to manage cancer risk.
8. Order by Survival: This button ranks selected strategies from lowest to highest probability of survival to age 70.

Continue to Decision Tool

xALP

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WHAT ?

Types of Risk-Reducing Mastectomy

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- Simple Mastectomy
- Skin-Sparing (SSM)
- Skin-Reducing Mastectomy
- Nipple-Sparing (NSM)

Type of mastectomy depends on:
- Whether there is to be immediate reconstruction
- Patient characteristics and preference

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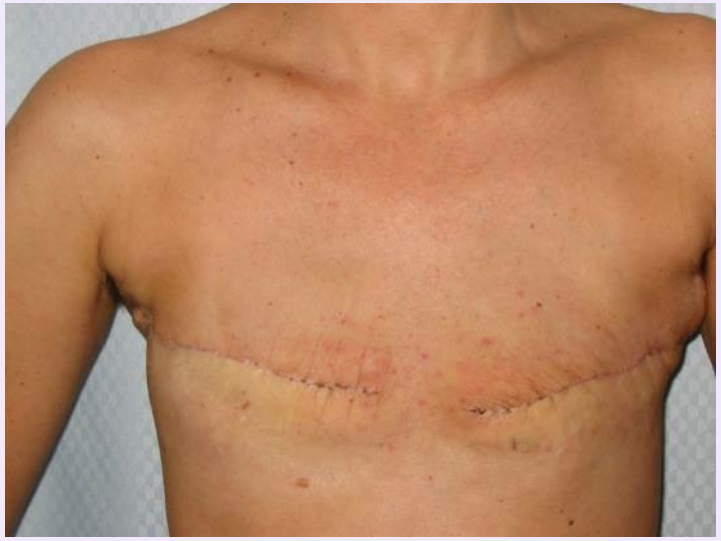
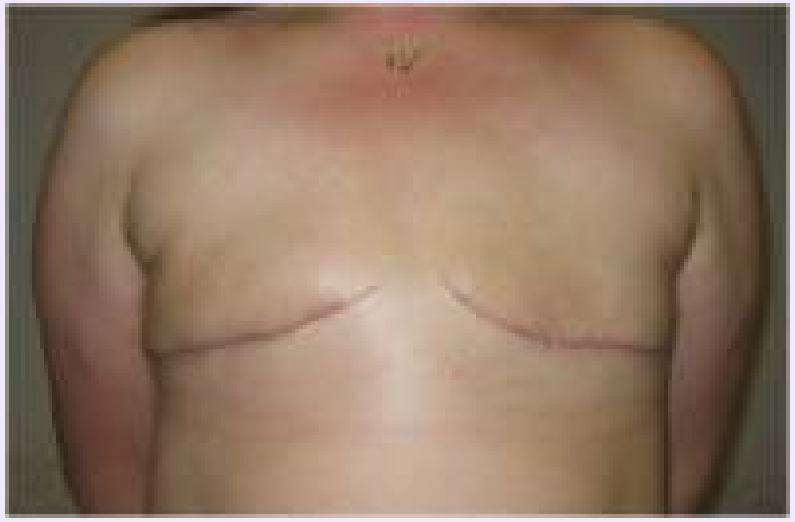
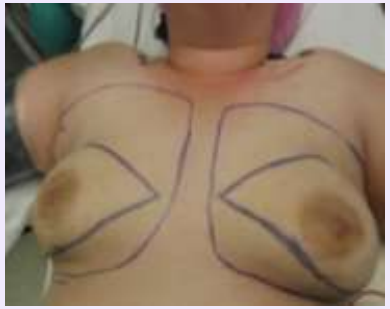
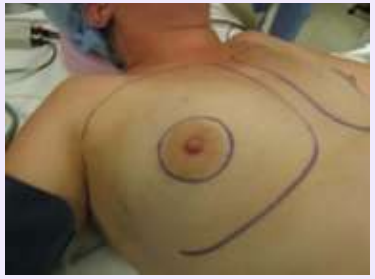
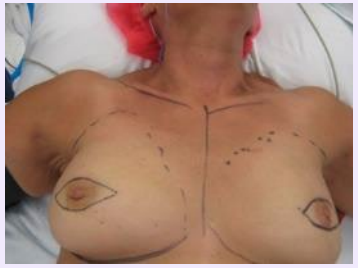
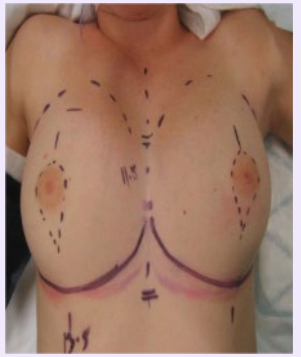
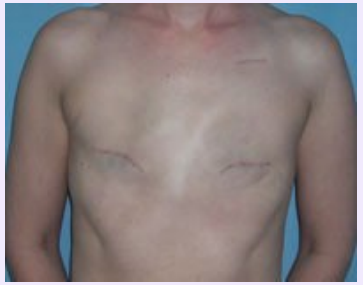
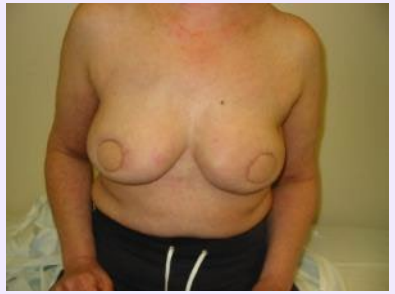
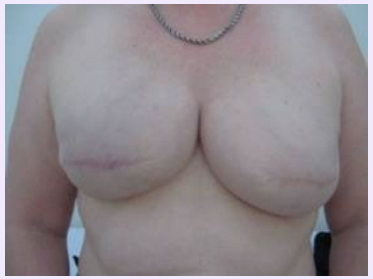
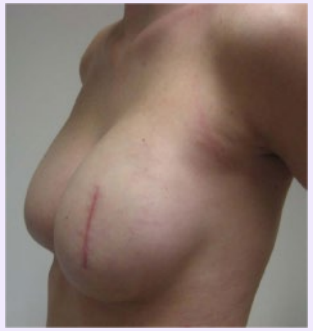
Simple Mastectomy

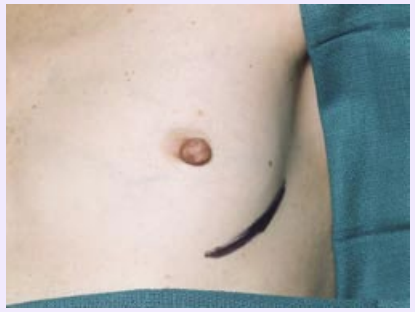
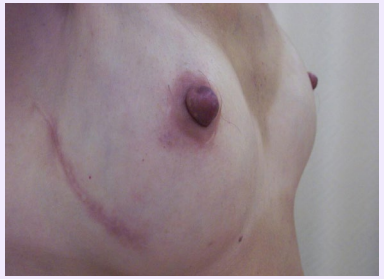
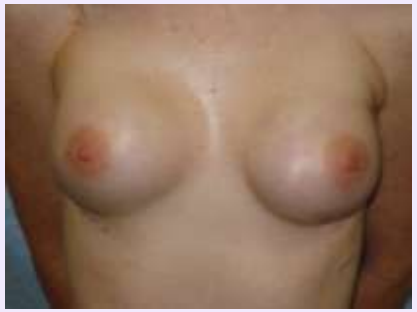
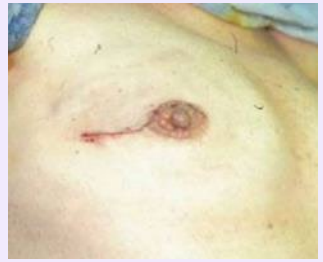




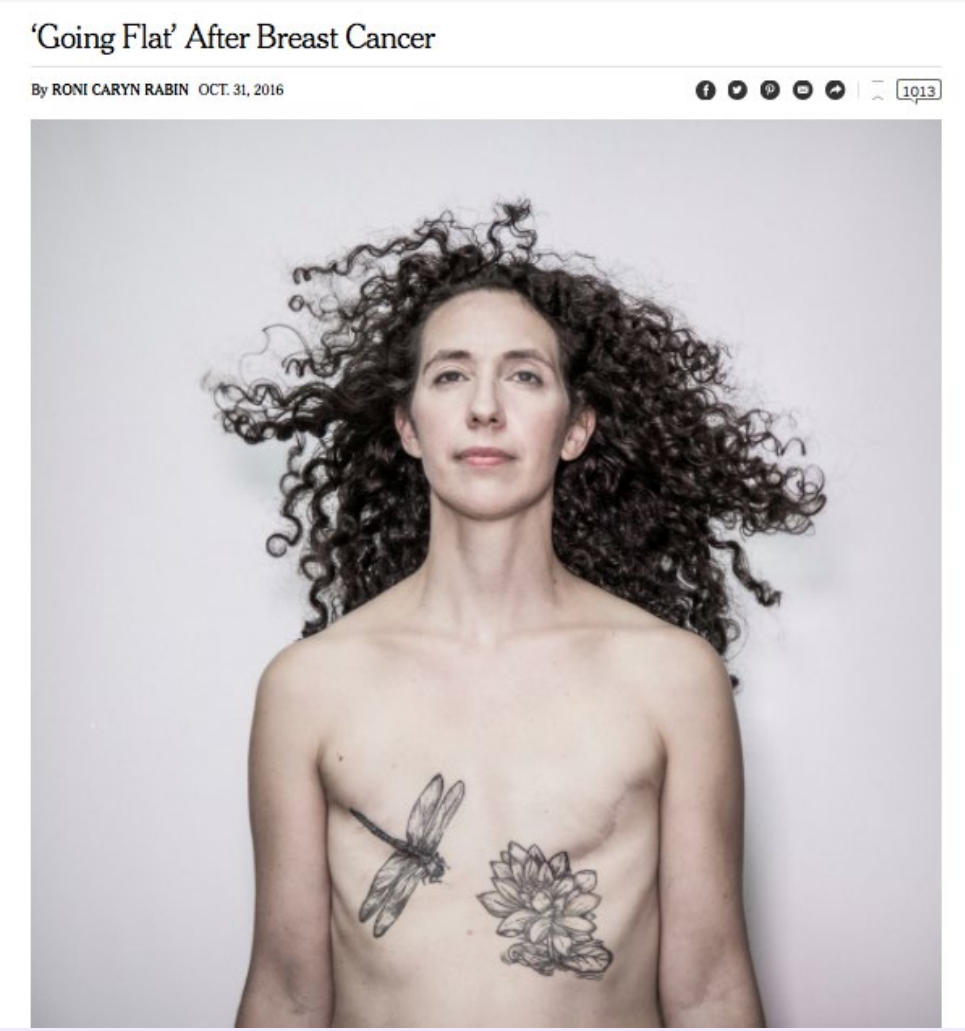
Simple Mastectomy

Skin-Sparing Mastectomy

Nipple-Sparing Mastectomy

"Going Flat"



New York Times, Oct 2016

http://www.flatandfabulous.org

International Reconstruction Rates Post Risk Reducing Mastectomy

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Ann Surg Oncol (2013) 20:3817–3822
DOI 10.1245/s10434-013-3040-4

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

ORIGINAL ARTICLE – BREAST ONCOLOGY

International Rates of Breast Reconstruction After Prophylactic Mastectomy in *BRCA1* and *BRCA2* Mutation Carriers

John Semple, MD[1], Kelly A. Metcalfe, RN, PhD[1,2], Henry T. Lynch, MD[3], Charmaine Kim-Sing, MD[4], Leigha Senter, MS, CGC[5], Tuya Pal, MD[6], Peter Ainsworth, MD[7], Jan Lubinski, MD, PhD[8], Nadine Tung, MD[9], Charis Eng, MD, PhD[10,11,12,13], Donna Gilchrist, MD[14], Joanne Blum, MD, PhD[15], Susan L. Neuhausen, PhD[16], Christian F. Singer, MD[17], Parviz Ghadirian, PhD[18], Ping Sun, PhD[1], Steven A. Narod, MD[1] and The Hereditary Breast Cancer Clinical Study Group

Ann Surg Onc 2013

- 70 % BRCA 1/ 2 mutation carriers have reconstruction after prophylactic mastectomy
- Compared to 5-29% of women having a mastectomy for breast cancer

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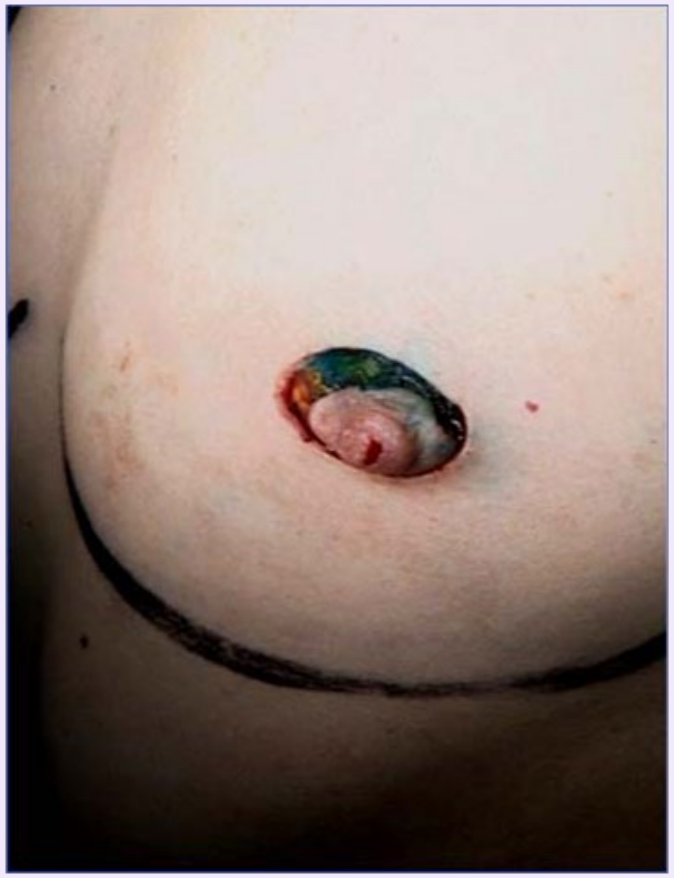
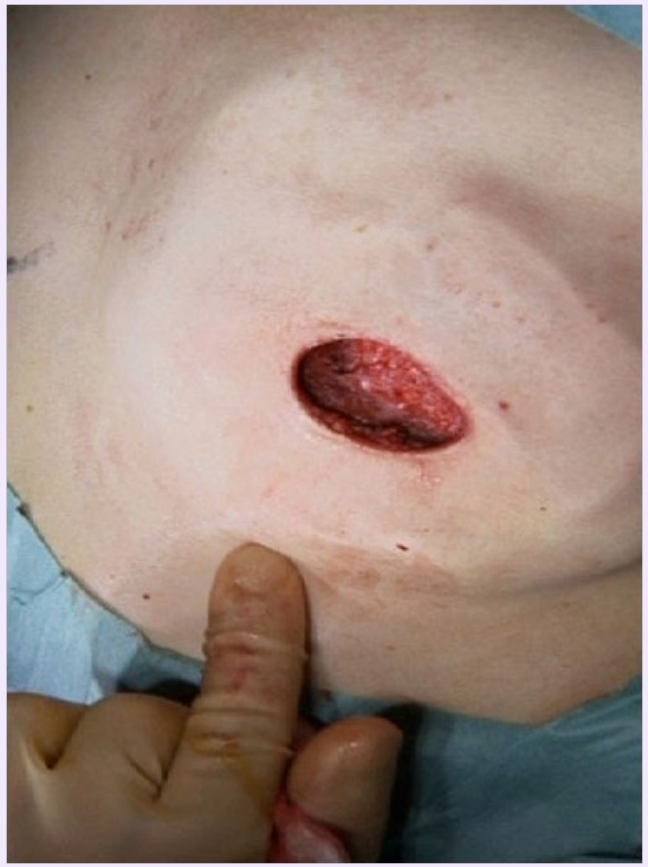
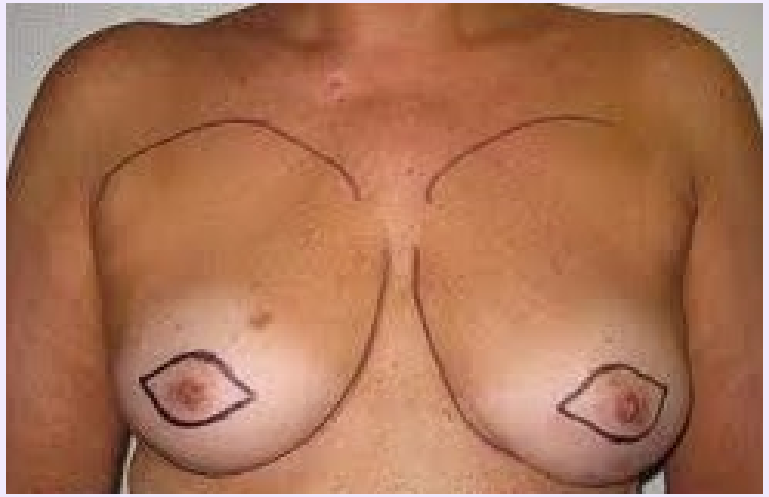
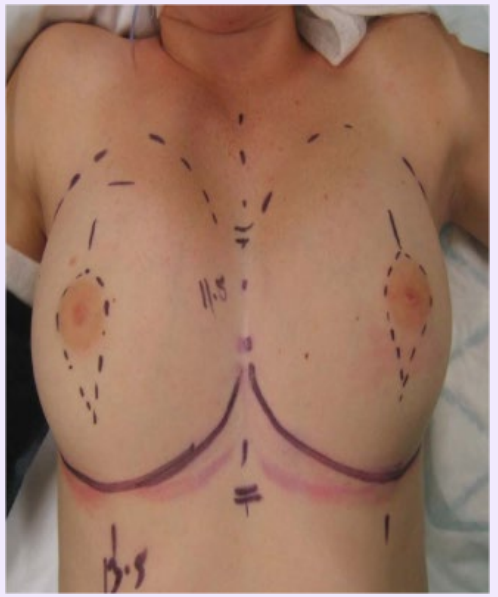
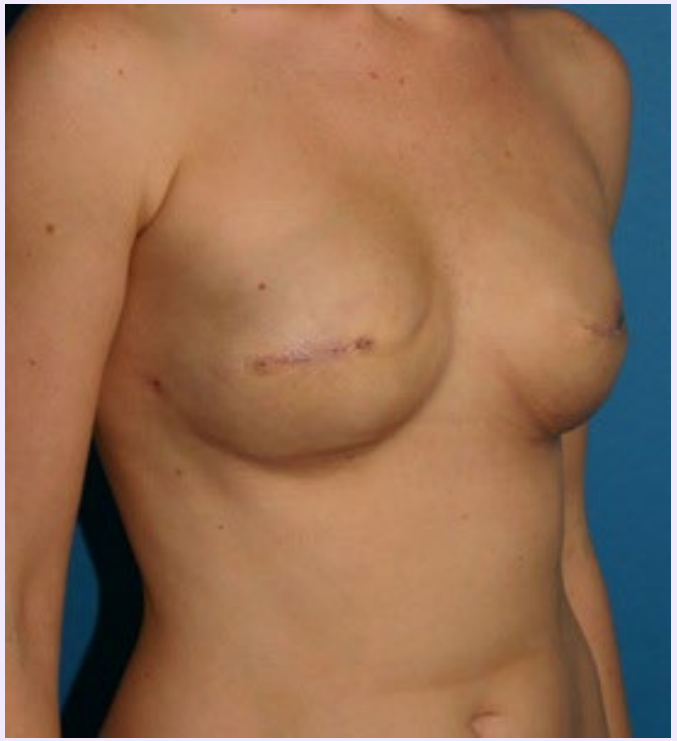
Skin-Sparing Mastectomy (SSM)

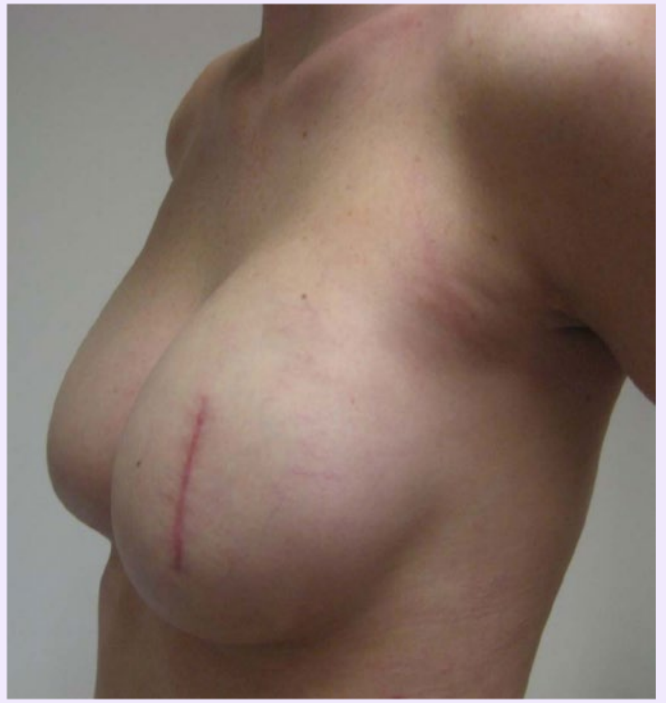












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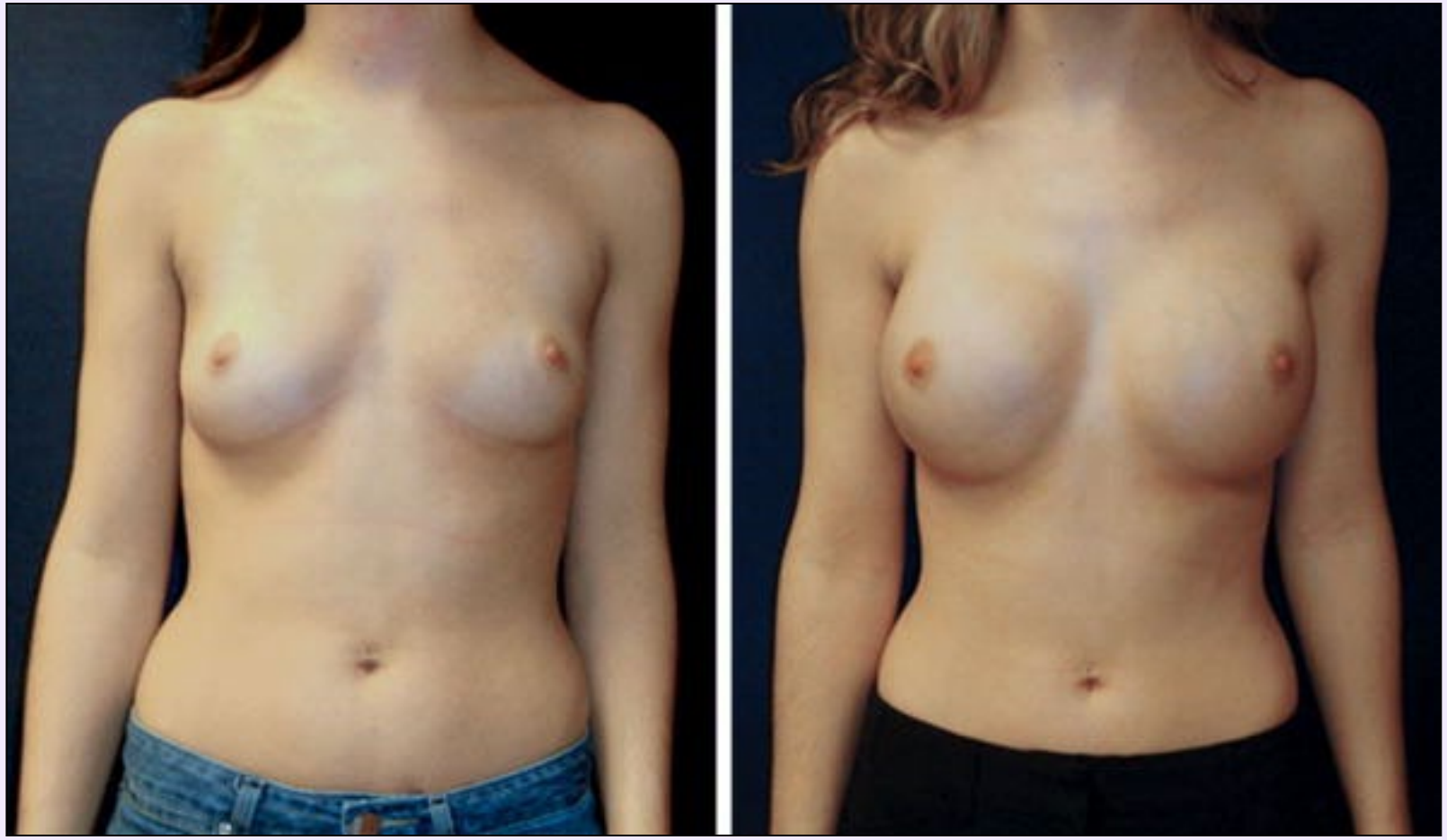
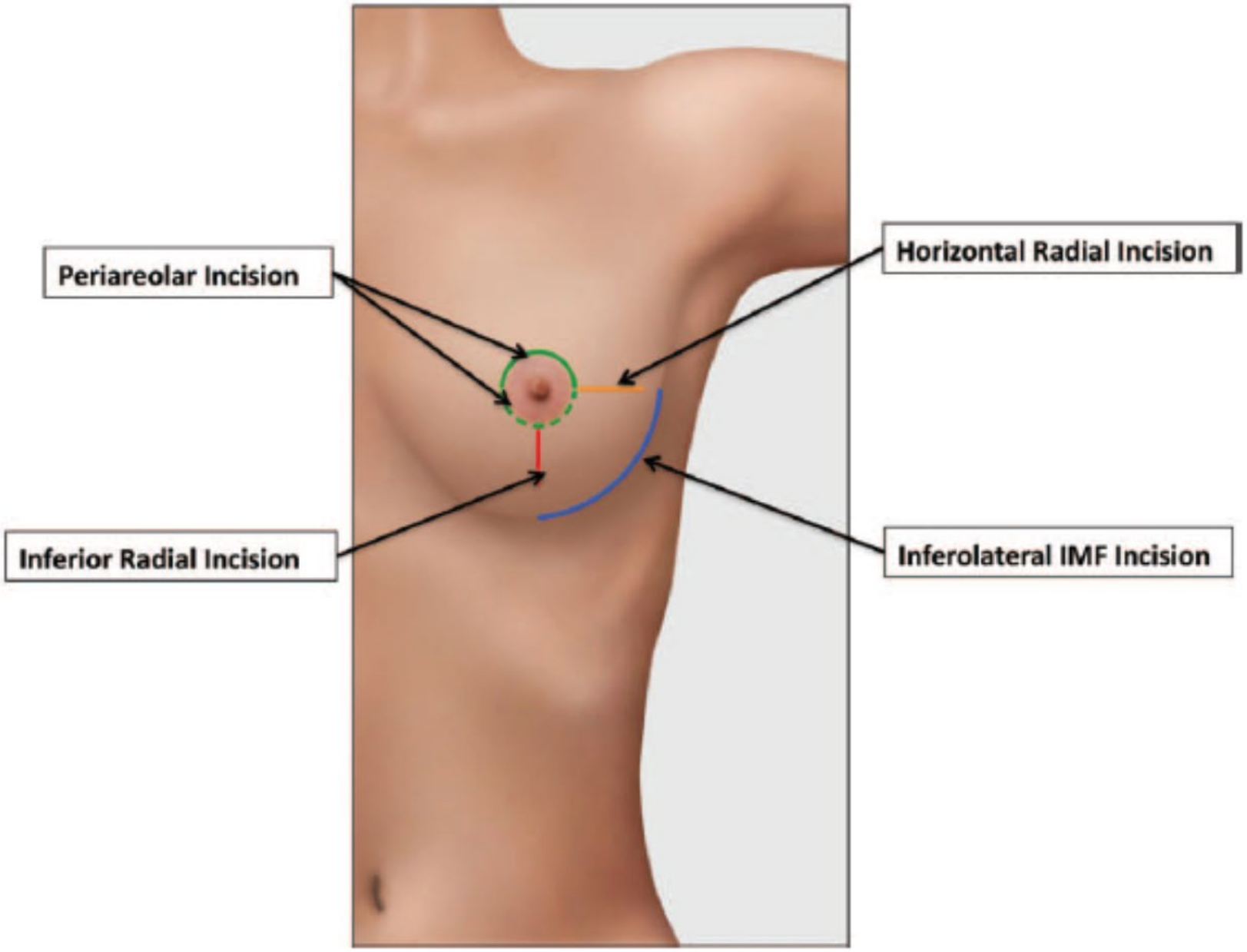
Nipple-Sparing Mastectomy (NSM)





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WHERE?

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BREAST SURGEONS of Australia & New Zealand | Australian Society of Plastic Surgeons | Breast Cancer Network Australia

Prioritising access to risk reducing surgery for people with inherited high risks of breast cancer

Australian Access to Breast Reconstruction Collaborative Group position statement

The Australian Access to Breast Reconstruction Collaborative Group (AABRCG) is dedicated to advocating for improved access to breast reconstruction services across Australia by bringing together primary care expertise and cancer policy and research. The group was established in 2020 as a partnership between Breast Surgeons of Australia and New Zealand (BreastSurgANZ), the Australian Society of Plastic Surgeons (ASPS), and Breast Cancer Network Australia (BCNA).

Breast cancer doesn't discriminate, but some people have at least a 70% risk of being diagnosed due to inherited genetic factors. The AABRCG advocates for all Australians at high risk of breast cancer to have timely access to life-changing risk reducing surgery (prophylactic mastectomy).

Currently, risk reducing surgeries are not consistently classified as semi-urgent elective surgeries in public health services. People with inherited risks of breast cancer often wait more than 12 months for these surgeries. They also face higher rates of emotional distress and generational trauma associated with cancer risk, and the possibility of premature death. Alternative pathways through the private health system can cost patients as much as $50,000, making it an impossible option for many.

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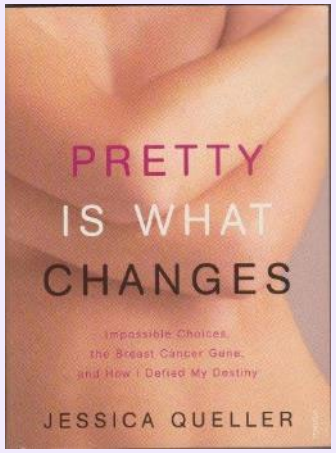
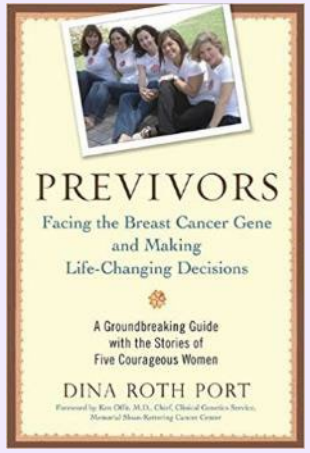
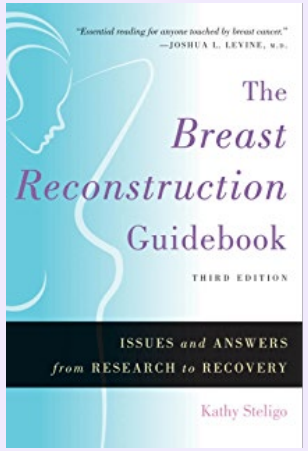
Resources

- Books
- Organisations
- Online Groups
- Social Media







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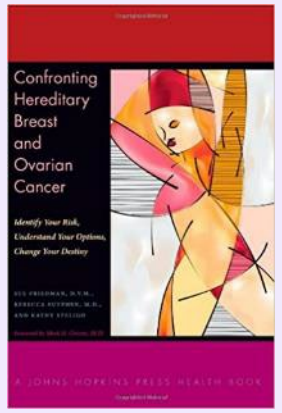

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FORCE Facing Hereditary Cancer EMPOWERED

Force

www.facingourrisk.org

bright pink

Bright Pink

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BASSER CENTER FOR BRCA

Basser Center for BRCA

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Patient Information

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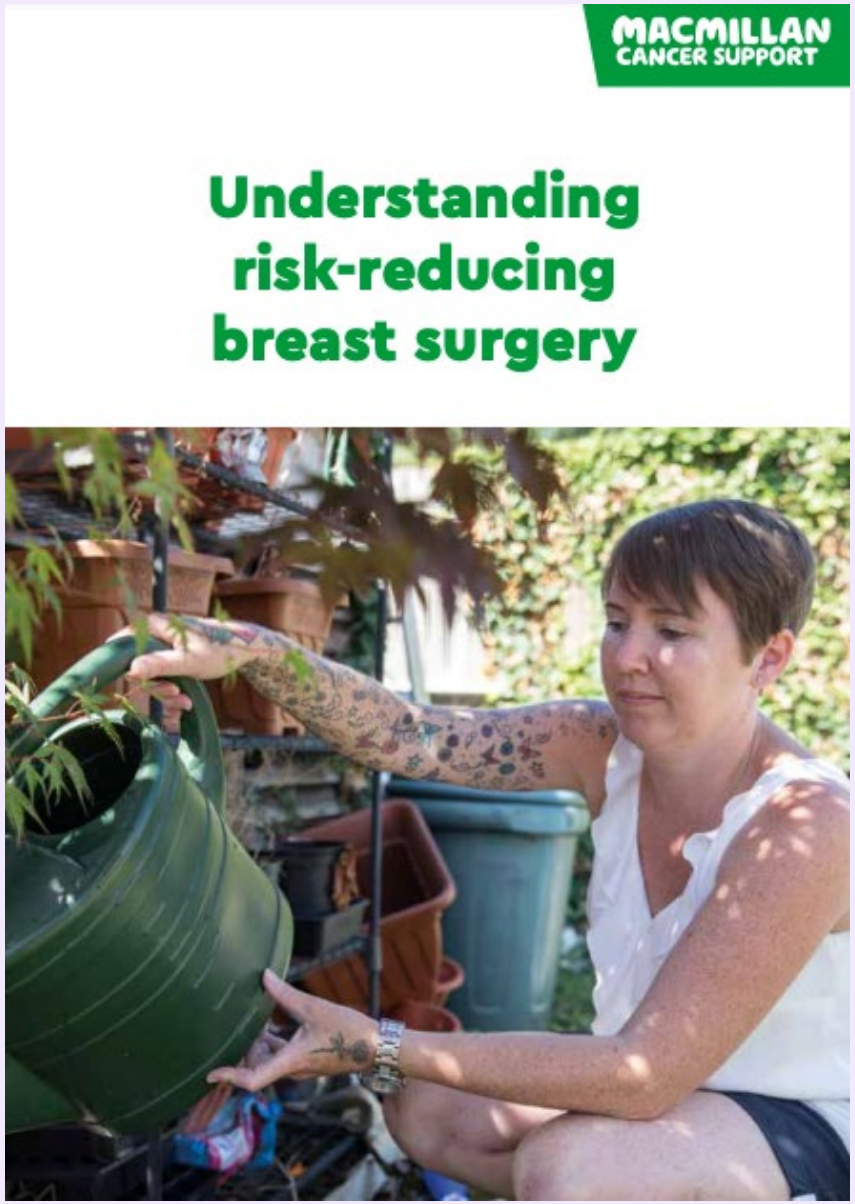

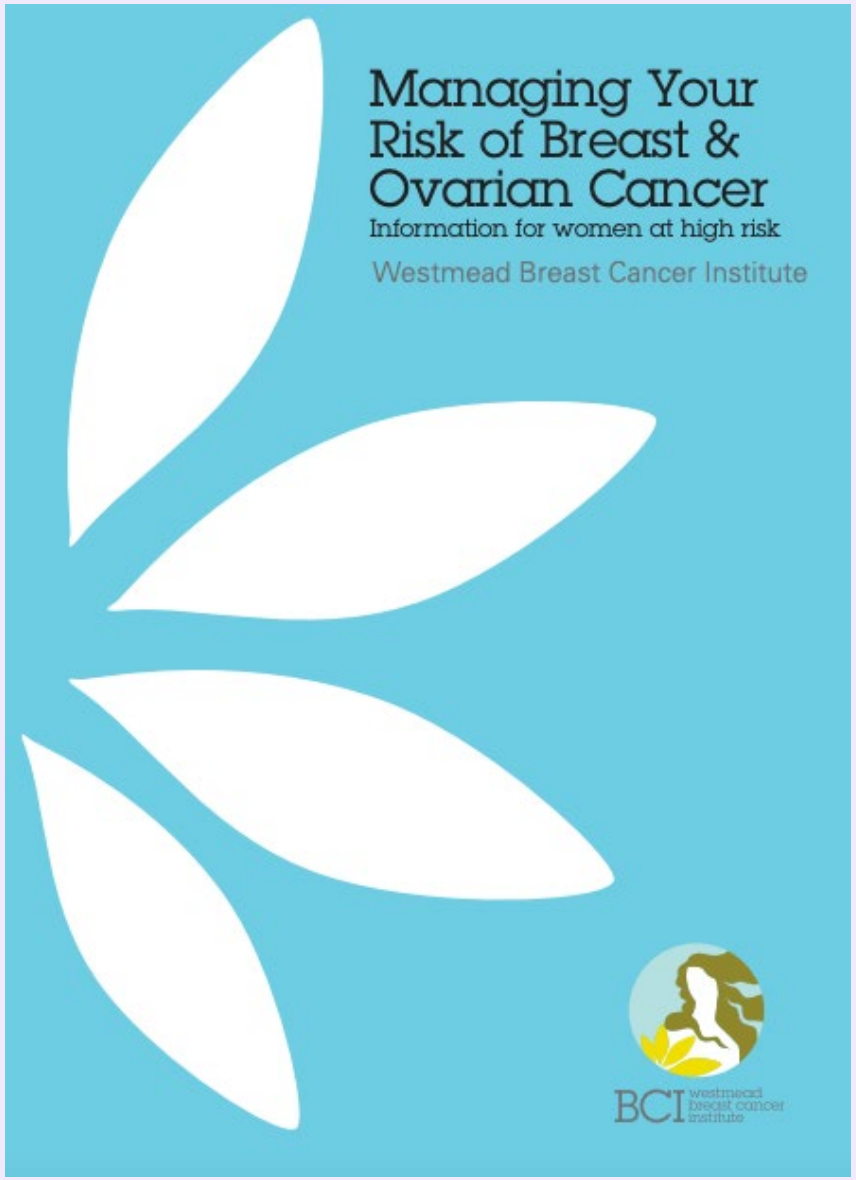

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Disinformation is defined as "false information that is spread with the specific intent of misleading or deceiving people".

- The FDA have published guidelines for communicating risks and benefits from research studies, which state that both the RRR and ARR should be reported to the public.

- Although RRRs were reported in the media and scientific journals by vaccine manufacturers and the FDA Advisory Committee that authorized and approved the COVID-19 mRNA vaccines, ARRs were not reported, denying the public important information needed before consenting to vaccination.

1.	Relative Risk	= Experimental Event Rate/Control Event Rate
2.	Relative Risk Reduction	= 1 – Relative Risk
3.	Absolute Risk Reduction	= Control Event Rate – Experimental Event Rate
4.	Relative Risk Reduction	= Absolute Risk Reduction/Control Event Rate
5.	Number Needed to Treat	= 1/ARR

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Risk Reduction Strategies in High-Risk Patients

REFERENCES

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Evidence for Breast Cancer Risks in Association with Various Pathogenic Gene Variants

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Research

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

IMPORTANCE The clinical management of *BRCA1* and *BRCA2* mutation carriers requires accurate, prospective cancer risk estimates.

OBJECTIVES To estimate age-specific risks of breast, ovarian, and contralateral breast cancer for mutation carriers and to evaluate risk modification by family cancer history and mutation location

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of 6036 *BRCA1* and 3820 *BRCA2* female carriers (5046 unaffected and 4810 with breast or ovarian cancer or both at baseline) recruited in 1997-2011 through the International *BRCA1/2* Carrier Cohort Study, the Breast Cancer Family Registry and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer, with ascertainment through family clinics (94%) and population-based studies (6%). The majority were from large national studies in the United Kingdom (EMBRACE), the Netherlands (HEBON), and France (GENEPSO). Follow-up ended December 2013; median follow-up was 5 years.

EXPOSURES *BRCA1/2* mutations, family cancer history, and mutation location.

MAIN OUTCOMES AND MEASURES Annual incidences, standardized incidence ratios, and cumulative risks of breast, ovarian, and contralateral breast cancer.

RESULTS Among 3886 women (median age, 38 years; interquartile range [IQR], 30-46 years) eligible for the breast cancer analysis, 5066 women (median age, 38 years; IQR, 31-47 years) eligible for the ovarian cancer analysis, and 2213 women (median age, 47 years; IQR, 40-55 years) eligible for the contralateral breast cancer analysis, 426 were diagnosed with breast cancer, 109 with ovarian cancer, and 245 with contralateral breast cancer during follow-up. The cumulative breast cancer risk to age 80 years was 72% (95% CI, 65%-79%) for *BRCA1* and 69% (95% CI, 61%-77%) for *BRCA2* carriers. Breast cancer incidences increased rapidly in early adulthood until ages 30 to 40 years for *BRCA1* and until ages 40 to 50 years for *BRCA2* carriers, then remained at a similar, constant incidence (20-30 per 1000 person-years) until age 80 years. The cumulative ovarian cancer risk to age 80 years was 44% (95% CI, 36%-53%) for *BRCA1* and 17% (95% CI, 11%-25%) for *BRCA2* carriers. For contralateral breast cancer, the cumulative risk 20 years after breast cancer diagnosis was 40% (95% CI, 35%-45%) for *BRCA1* and 26% (95% CI, 20%-33%) for *BRCA2* carriers (hazard ratio [HR] for comparing *BRCA2* vs *BRCA1*, 0.62; 95% CI, 0.47-0.82; *P*=.001 for difference). Breast cancer risk increased with increasing number of first- and second-degree relatives diagnosed as having breast cancer for both *BRCA1* (HR for ≥2 vs 0 affected relatives, 1.99; 95% CI, 1.41-2.82; *P*<.001 for trend) and *BRCA2* carriers (HR, 1.91; 95% CI, 1.08-3.37; *P*=.02 for trend). Breast cancer risk was higher if mutations were located outside vs within the regions bounded by positions c.2282-c.4071 in *BRCA1* (HR, 1.46; 95% CI, 1.11-1.93; *P*=.007) and c.2831-c.6401 in *BRCA2* (HR, 1.93; 95% CI, 1.36-2.74; *P*<.001).

CONCLUSIONS AND RELEVANCE These findings provide estimates of cancer risk based on *BRCA1* and *BRCA2* mutation carrier status using prospective data collection and demonstrate the potential importance of family history and mutation location in risk assessment.

JAMA. 2017;317(23):2402-2416

Table 4. Hazard Ratio Estimates for Breast and Ovarian Cancer Associated With Family History of Breast or Ovarian Cancer in First- and Second-Degree Relatives and Corresponding Cumulative Risk Estimates

Family History Category	No. of Women	No. of Person-Years	No. of Events	Hazard Ratio (95% CI)	*P* Value	Cumulative Risk by Age, % (95% CI)			
						40 y	50 y	60 y	70 y
Breast cancer risk for *BRCA1* mutation carriers									
No breast cancers	600	3283	54	1 [Reference]		16 (10-23)	35 (27-44)	43 (34-53)	53 (39-69)
1 breast cancer	719	4176	91	1.51 (1.08-2.11)	.02	27 (21-35)	47 (40-55)	56 (48-64)	68 (59-77)
≥2 breast cancers	737	3864	108	1.99 (1.41-2.82)	<.001	31 (23-40)	50 (42-58)	67 (60-75)	73 (65-80)
Family history unknown	205	906	13	1.06 (0.54-2.08)	.86				
Cancer type unknown in family	15	128	3	2.57 (1.16-5.71)	.02				
≥1 breast cancers	1456	8040	199	1.67 (1.23-2.26)	.001	28 (23-34)	48 (43-54)	62 (57-68)	71 (66-80)
Per affected relative with breast cancer				1.15 (1.07-1.24)	<.001				
Breast cancer risk for *BRCA2* mutation carriers									
No breast cancers	302	1499	17	1 [Reference]		5 (1-18)	26 (16-40)	39 (25-56)	39 (25-56)
1 breast cancer	495	2675	49	1.53 (0.86-2.70)	.15	14 (8-24)	30 (21-41)	55 (44-67)	62 (51-74)
≥2 breast cancers	634	3112	78	1.91 (1.08-3.37)	.02	14 (8-24)	40 (32-50)	57 (48-66)	65 (56-74)
Family history unknown	166	575	13	1.82 (0.80-4.14)	.15				
Cancer type unknown in family	13	53	0						
≥1 breast cancers	1129	5787	127	1.69 (0.99-2.88)	.05	14 (9-21)	36 (30-43)	56 (49-63)	64 (57-71)
Per affected relative with breast cancer				1.15 (1.02-1.30)	.02				
Ovarian cancer risk for *BRCA1* mutation carriers									
No ovarian cancers	1706	8774	46	1 [Reference]		2 (1-4)	7 (4-11)	15 (10-21)	41 (30-53)
1 ovarian cancer	689	3286	21	1.24 (0.75-2.03)	.40	1 (0-6)	11 (6-20)	27 (16-43)	45 (30-64)
≥2 Ovarian cancers	228	1117	12	1.77 (0.90-3.46)	.10	5 (1-18)	15 (7-31)	40 (23-62)	45 (27-67)
Family history unknown	230	1000	4	1.08 (0.36-3.23)	.90				
Cancer type unknown in family	52	368	2	1.21 (0.29-5.07)	.79				
≥1 ovarian cancers	917	4403	33	1.37 (0.89-2.11)	.16	2 (1-6)	12 (8-20)	31 (22-43)	44 (32-58)
Per affected relative with ovarian cancer				1.20 (0.94-1.55)	.15				
Ovarian cancer risk for *BRCA2* mutation carriers									
No ovarian cancers	1558	7845	18	1 [Reference]		0	0	6 (3-12)	16 (10-25)
1 ovarian cancer[a]	331	1463	4	1.26 (0.43-3.69)	.67				
≥2 Ovarian cancers	55	215	1						
Family history unknown	169	558	1	0.83 (0.10-6.70)	.87				
Cancer type unknown in family	48	257	0						
≥1 ovarian cancers	386	1678	5	1.09 (0.37-3.25)	.87	1 (0-10)	1 (1-10)	8 (2-26)	15 (5-39)
Per affected relative with ovarian cancer				0.94 (0.39-2.26)	.90				

[a] Numbers too small to obtain estimates.

Key Points

Question What are the breast and ovarian cancer risks for *BRCA1* and *BRCA2* mutation carriers and are they related to family history of cancer and mutation position?

Findings From a prospective cohort of 9856 mutation carriers, mainly ascertained through cancer genetic clinics, the cumulative breast cancer risk to age 80 years was 72% for *BRCA1* and 69% for *BRCA2* carriers. The cumulative ovarian cancer risk to age 80 years was 44% for *BRCA1* and 17% for *BRCA2* carriers. Cancer risks differed by cancer family history and mutation position.

Meaning These findings provide cancer risk patterns based on *BRCA* status using prospective data. Family history and mutation position are important additional variables in risk assessment.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

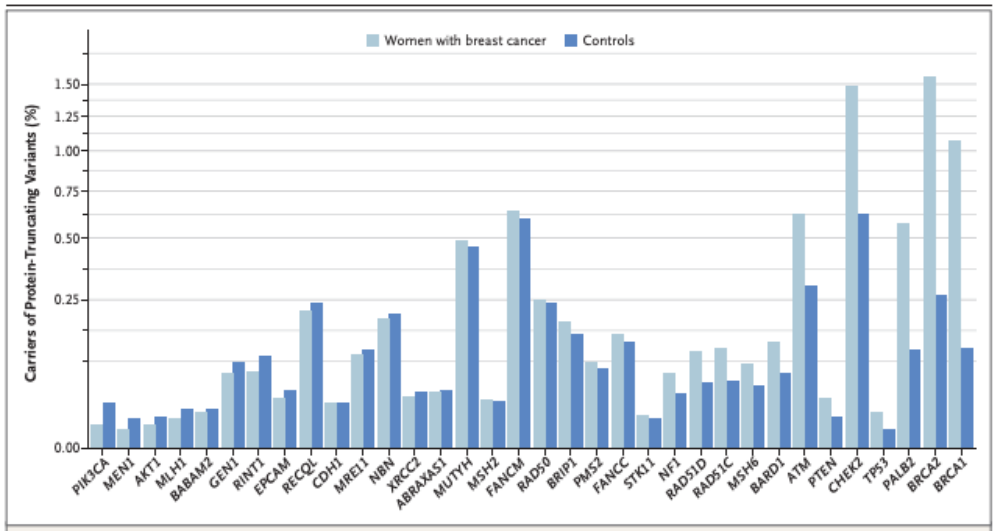

Figure 1. Frequency of Protein-Truncating Variants in 34 Genes in Population-Based Studies.
Shown are percentages of women with breast cancer and controls who were carriers of protein-truncating variants in 34 genes. The genes are listed in order of increasing estimated odds ratios for breast cancer overall.

BACKGROUND

Genetic testing for breast cancer susceptibility is widely used, but for many genes, evidence of an association with breast cancer is weak, underlying risk estimates are imprecise, and reliable subtype-specific risk estimates are lacking.

METHODS

We used a panel of 34 putative susceptibility genes to perform sequencing on samples from 60,466 women with breast cancer and 53,461 controls. In separate analyses for protein-truncating variants and rare missense variants in these genes, we estimated odds ratios for breast cancer overall and tumor subtypes. We evaluated missense-variant associations according to domain and classification of pathogenicity.

RESULTS

Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a risk of breast cancer overall with a P value of less than 0.0001. Protein-truncating variants in 4 other genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*) were associated with a risk of breast cancer overall with a P value of less than 0.05 and a Bayesian false-discovery probability of less than 0.05. For protein-truncating variants in 19 of the remaining 25 genes, the upper limit of the 95% confidence interval of the odds ratio for breast cancer overall was less than 2.0. For protein-truncating variants in *ATM* and *CHEK2*, odds ratios were higher for estrogen receptor (ER)–positive disease than for ER-negative disease; for protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative disease than for ER-positive disease. Rare missense variants (in aggregate) in *ATM*, *CHEK2*, and *TP53* were associated with a risk of breast cancer overall with a P value of less than 0.001. For *BRCA1*, *BRCA2*, and *TP53*, missense variants (in aggregate) that would be classified as pathogenic according to standard criteria were associated with a risk of breast cancer overall, with the risk being similar to that of protein-truncating variants.

CONCLUSIONS

The results of this study define the genes that are most clinically useful for inclusion on panels for the prediction of breast cancer risk, as well as provide estimates of the risks associated with protein-truncating variants, to guide genetic counseling. (Funded by European Union Horizon 2020 programs and others.)

N Engl J Med 384;5 February 4, 2021

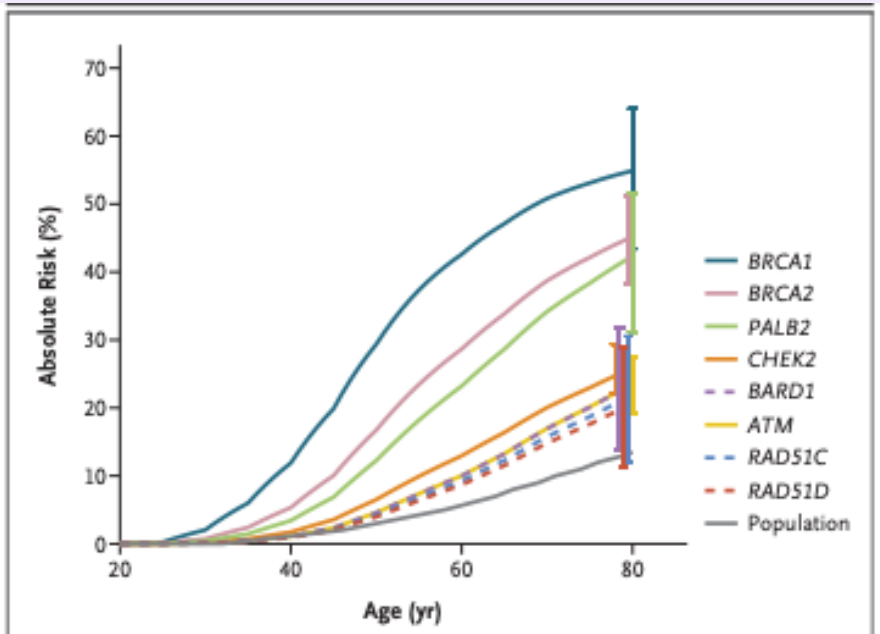

Figure 3. Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.

Shown are absolute risks of breast cancer through 80 years of age associated with protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. The absolute risk was not calculated for *TP53* because of the wide 95% confidence interval for the odds ratio and the known association with a substantial risk of childhood cancer. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016.[6] The I bars indicate 95% confidence intervals.

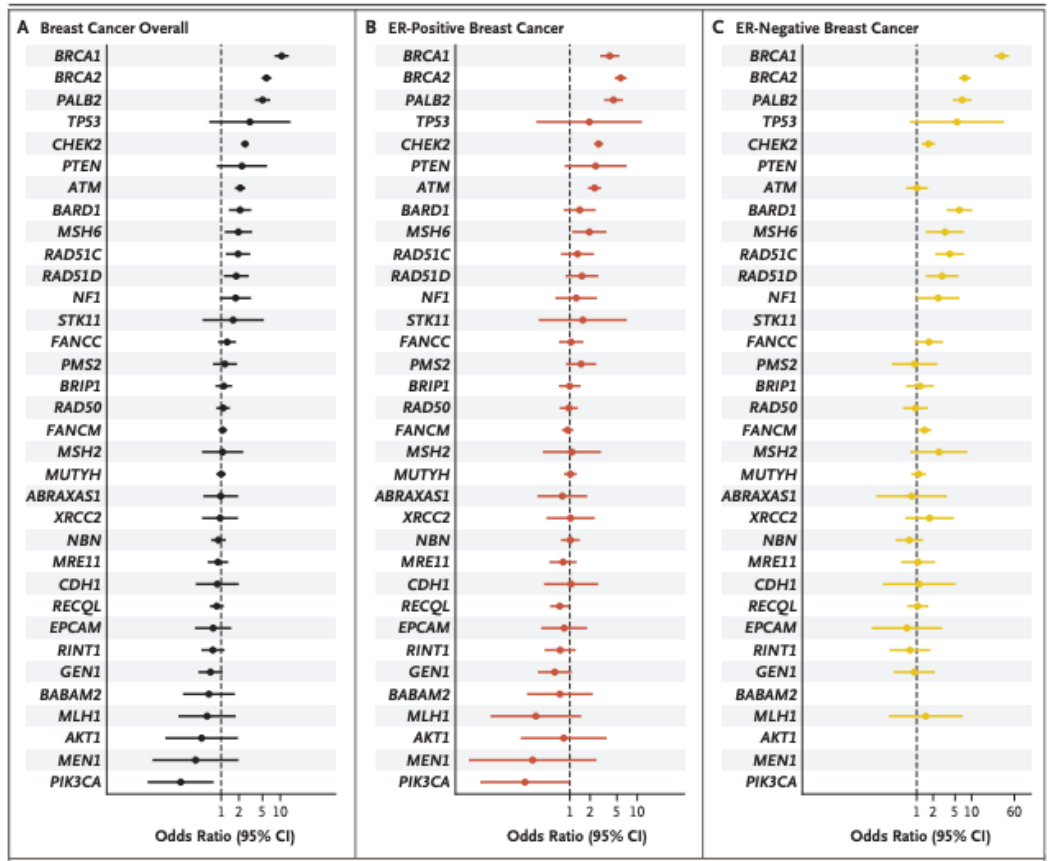

Figure 2. Risk of Breast Cancer Overall and Tumor Subtypes Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies.

Shown are odds ratios and 95% confidence intervals (CIs) for breast cancer overall (Panel A), estrogen receptor (ER)–positive breast cancer (Panel B), and ER-negative breast cancer (Panel C) associated with protein-truncating variants in 34 genes. The genes are listed in order of decreasing estimated odds ratios for breast cancer overall.

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Screening/Early Detection

Evidence for Clinical Breast Examination (CBE) in High-Risk Women

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Research

The value of clinical breast examination in a breast cancer surveillance program for women with germline *BRCA1* or *BRCA2* mutations

Tamara Hettipathirana[1,2], Courtney Macdonald[2], Jing Xie[2], Kate Moodie[2], Chris Michael[2], Kelly-Anne Phillips[1,2]

4 Performance of clinical breast examination for the 414 women included in the study

Breast examination result abnormal, imaging results normal	Breast cancer diagnosis: Yes	Breast cancer diagnosis: No	
Yes	2*	12	Positive predictive value: 14%
No	33	367	Negative predictive value: 92%
	Sensitivity: 6%	Specificity: 97%	

* Results of imaging tests at follow-up visit were normal.

The known: Reflecting the uncertain evidence base, guidelines offer conflicting advice about the value of clinical breast examination for breast cancer surveillance of women with *BRCA1/2* mutations.

The new: We found that the sensitivity of clinical breast examination for detecting cancers was very low. It is not useful for the surveillance of women with *BRCA1/2* mutations undergoing routine MRI screening.

The implications: Clinical breast examination can safely be omitted from breast cancer screening of women with *BRCA1/2* mutations. This could reduce consultation times and facilitate the use of telehealth.

Abstract

Objective: To assess the sensitivity and specificity of clinical breast examination for detecting breast cancer in asymptomatic women with predisposing germline mutations enrolled in a cancer risk management program that includes radiologic screening.

Design, setting: Retrospective, longitudinal cohort study of women with *BRCA1/2* mutations who attended the Breast and Ovarian Cancer Risk Management Clinic at the Peter MacCallum Cancer Centre, a tertiary referral centre in Melbourne, during 1 September 2001 – 31 December 2019.

Participants: Consecutive women with *BRCA1/2* mutations who did not have personal histories of cancer and had not undergone bilateral risk-reducing mastectomy, and who had visited the clinic at least twice during the study period. Participants had generally undergone breast examination at 6- or 12-month intervals, and annual breast imaging (mammography; and magnetic resonance imaging [MRI] for women aged 50 years or younger).

Main outcome measures: Sensitivity (proportion of all biopsy-confirmed breast cancers detected by breast examination alone) and specificity of breast examination for detecting breast cancer.

Results: Of 414 eligible women (mean age, 35.5 years; SD, 11.2 years), 35 were diagnosed with breast cancer during 1761 woman-years of follow-up. Only two were diagnosed based on breast examination alone (ie, without radiologic evidence), neither of whom was undergoing MRI screening. The sensitivity of breast examination was 6% (95% CI, 1–19%), the specificity 97% (95% CI, 95–98%); the positive predictive value was 14% (95% CI, 2–43%), the negative predictive value 92% (95% CI, 89–94%).

Conclusion: Clinical breast examination did not increase the number of breast cancers detected in MRI-screened women with *BRCA1/2* mutations. Removing breast examination from surveillance programs that include MRI may be reasonable for these women.

MJA 215 (10) ▪ 15 November 2021

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Evidence for MRI Screening of Women at High Risk of Breast Cancer

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Magnetic Resonance Imaging in Screening of Breast Cancer

Yiming Gao, MD[a,*], Beatriu Reig, MD, MPH[a], Laura Heacock, MS, MD[a], Debbie L. Bennett, MD[b], Samantha L. Heller, PhD, MD[a], Linda Moy, MD[a,c,d]

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KEY POINTS

- Magnetic resonance (MR) imaging has a modality-based advantage compared to mammography and sonography in early detection of invasive breast cancer, which is being leveraged to optimize screening outcomes.
- Supplemental screening with MR imaging has been found to be of value in high-risk women as well as in certain subgroups of higher-than-average-risk women, but careful cost-benefit considerations are needed.
- Overall adherence to MR imaging among currently eligible women is poor even as screening indications of MR imaging continue to evolve.

Radiol Clin N Am 59 (2021) 85–98

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Table 1
Comparison of diagnostic performance using magnetic resonance imaging versus mammography or sonography in multimodality breast cancer screening among high-risk women based on outcomes of prospective studies

				Sensitivity			Specificity			PPV_3			
Reference	Patients (n)	Rounds (n)[a]	Inclusion	MR Imaging (%)	MG (%)	US (%)	MR Imaging (%)	MG (%)	US (%)	MR Imaging (%)	MG (%)	US (%)	Interval CA (n)
2020[11]	8782	20,053	BRCA+/Fam	91	41	NA	87	92	NA	20	26	NA	12
2019[12,b]	674	2812	Fam	98	87	NA	84	91	NA	27	28	NA	1
2017[13]	296	1170	BRCA+/Fam	68	37	32	95	98	95	25	34	10	3
2015[22]	559	1506	BRCA+/Fam	90	38	38	89	97	97	20	28	27	1
2014[23]	221	1855	BRCA+	100	27	77	56	82	84	NA	NA	NA	1
2012[26]	612	612	Mixed/Dense	88	52	45	76	91	90	23	38	12	9
2011[3]	501	1592	BRCA+/Fam	91	50	52	97	99	98	56	71	62	3
2010[4]	687	1679	BRCA+/Fam	93	33	37	98	99	98	48	39	36	0

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Table 2
Multidisciplinary recommendations for annual supplemental magnetic resonance imaging screening in higher-than-average-risk women

Organization	BRCA Carriers/ First-Degree Relatives[a]	Family History	Prior Radiation	Personal History	Dense Tissue	History of Atypia[b]
ACS 2007	BRCA1/2/select mutations	If LTR ≥20%	Age 10–30 y	NR	NR	NR
ACR 2018	BRCA1/2/select mutations	If LTR ≥20%	Age<30 y	If early diagnosis (before age 50)	If personal history (prior breast cancer)	If other risk factors
ASBrS 2019	BRCA1/2/select mutations	If strong family history	Age 10–30 y	If early diagnosis (before age 50 y)	If personal history (prior breast cancer)	NR
NCCN 2020	BRCA1/2/select mutations	If family history suggests hereditary pattern despite absence of mutation (eg, early diagnosis before age 30 y)	Age<30 y	NR	NR	If LTR ≥20%
EUSOBI 2015	BRCA1/2/select mutations	Selective	Age<30 y	NR	NR	NR
ECIBS 2020[c]	NS	NR	NS	NS	NR	NR
ACOG 2017	BRCA1/2/select mutations	If LTR ≥20%	Age 10–30 y	If other risks	NR	NR

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Risk-Reduction

Evidence for Lifestyle Modification

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RESEARCH ARTICLE Open Access

Age-specific breast cancer risk by body mass index and familial risk: prospective family study cohort (ProF-SC)

John L. Hopper[1*], Gillian S. Dite[1], Robert J. MacInnis[1,2], Yuyan Liao[3], Nur Zeinomar[3], Julia A. Knight[4,5], Melissa C. Southey[6,21], Roger L. Milne[1,2], Wendy K. Chung[7,8], Graham G. Giles[1,2], Jeanine M. Genkinger[3], Sue-Anne McLachlan[9,10], Michael L. Friedlander[11,12], Antonis C. Antoniou[13], Prue C. Weideman[1], Gord Glendon[4], Stephanie Nesci[14], kConFab Investigators[15,16], Irene L. Andrulis[4,17], Saundra S. Buys[18], Mary B. Daly[19], Esther M. John[20], Kelly Anne Phillips[1,14,15] and Mary Beth Terry[3,7*]

Results: The strength and direction of the BMI risk association depended on baseline menopausal status ($P < 0.001$); after adjusting for menopausal status, the association did not depend on age at baseline ($P = 0.6$). In terms of absolute risk, the negative association with BMI for premenopausal women has a much smaller influence than the positive association with BMI for postmenopausal women. Women at higher familial risk have a much larger difference in absolute risk depending on their BMI than women at lower familial risk.

Conclusions: The greater a woman's familial risk, the greater the influence of BMI on her absolute postmenopausal breast cancer risk. Given that age-adjusted BMI is correlated across adulthood, maintaining a healthy weight throughout adult life is particularly important for women with a family history of breast cancer.

Breast Cancer Research (2018) 20:132

POPULATION AND PREVENTION SCIENCE | JANUARY 03 2020

Recreational Physical Activity Is Associated with Reduced Breast Cancer Risk in Adult Women at High Risk for Breast Cancer: A Cohort Study of Women Selected for Familial and Genetic Risk

Rebecca D. Kehm; Jeanine M. Genkinger; Robert J. MacInnis; Esther M. John; Kelly-Anne Phillips; Gillian S. Dite; Roger L. Milne; Nur Zeinomar; Yuyan Liao; Julia A. Knight; Melissa C. Southey; Wendy K. Chung; Graham G. Giles; Sue-Anne McLachlan; Kristen D. Whitaker; Michael Friedlander; Prue C. Weideman; Gord Glendon; Stephanie Nesci; kConFab Investigators; Irene L. Andrulis; Saundra S. Buys; Mary B. Daly; John L. Hopper; Mary Beth Terry

Abstract

Although physical activity is associated with lower breast cancer risk for average-risk women, it is not known if this association applies to women at high familial/genetic risk. We examined the association of recreational physical activity (self-reported by questionnaire) with breast cancer risk using the Prospective Family Study Cohort, which is enriched with women who have a breast cancer family history (*N* = 15,550). We examined associations of adult and adolescent recreational physical activity (quintiles of age-adjusted total metabolic equivalents per week) with breast cancer risk using multivariable Cox proportional hazards regression, adjusted for demographics, lifestyle factors, and body mass index. We tested for multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with *BRCA1* and *BRCA2* mutation status. Baseline recreational physical activity level in the highest four quintiles compared with the lowest quintile was associated with a 20% lower breast cancer risk (HR, 0.80; 95% confidence interval, 0.68–0.93). The association was not modified by familial risk or *BRCA* mutation status (*P* interactions >0.05). No overall association was found for adolescent recreational physical activity. Recreational physical activity in adulthood may lower breast cancer risk for women across the spectrum of familial risk.

Significance:

These findings suggest that physical activity might reduce breast cancer risk by about 20% for women across the risk continuum, including women at higher-than-average risk due to their family history or genetic susceptibility.

Cancer Res (2020) 80 (1): 116–125.

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Evidence for Risk-Reducing Medications

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Medication Use to Reduce Risk of Breast Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

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Table. Benefits and Harms of Risk-Reducing Medications Estimated From Meta-analysis of Randomized, Placebo-Controlled Trials[a,b]

Outcome	Tamoxifen	Raloxifene	Aromatase Inhibitors
Benefits: Events Reduced (95% CI)[c]			
Breast cancer			
Invasive	7 (4-12)	9 (3-15)	16 (8-24)
ER+	8 (4-13)	8 (4-13)	15 (8-20)
ER−	ND	ND	ND
Noninvasive	ND	ND	ND
Mortality			
Breast cancer	ND	NR	NR
All-cause	ND	ND	ND
Fracture			
Vertebral	ND	7 (5-9)	ND
Nonvertebral	3 (0.2-5)	ND	ND
Harms: Events Increased (95% CI)[c]			
Vascular			
Venous thromboembolic event	5 (2-9)	7 (0.3-17)	ND
Deep vein thrombosis	ND	ND	NR
Pulmonary embolism	ND	ND	NR
Coronary heart disease events	ND	ND	ND
Other			
Endometrial cancer	4 (1-8)	ND	ND
Cataracts	26 (5-50)[d]	ND	ND

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects. (B recommendation) The USPSTF recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer. (D recommendation) This recommendation applies to asymptomatic women 35 years and older, including women with previous benign breast lesions on biopsy (such as atypical ductal or lobular hyperplasia and lobular carcinoma in situ). This recommendation does not apply to women who have a current or previous diagnosis of breast cancer or ductal carcinoma in situ.

JAMA. 2019;322(9):857-867

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Evidence for Efficacy of Bilateral Risk-Reduction Mastectomy (BRRM) in Reducing Breast Cancer Risk

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EFFICACY OF BILATERAL PROPHYLACTIC MASTECTOMY IN WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

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N Engl J Med 1999;340:77-84.

ABSTRACT

Background Options for women at high risk for breast cancer include surveillance, chemoprevention, and prophylactic mastectomy. The data on the outcomes for surveillance and prophylactic mastectomy are incomplete.

Methods We conducted a retrospective study of all women with a family history of breast cancer who underwent bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. The women were divided into two groups — high risk and moderate risk — on the basis of family history. A control study of the sisters of the high-risk probands and the Gail model were used to predict the number of breast cancers expected in these two groups in the absence of prophylactic mastectomy.

Results We identified 639 women with a family history of breast cancer who had undergone bilateral prophylactic mastectomy: 214 at high risk and 425 at moderate risk. The median length of follow-up was 14 years. The median age at prophylactic mastectomy was 42 years. According to the Gail model, 37.4 breast cancers were expected in the moderate-risk group; 4 breast cancers occurred (reduction in risk, 89.5 percent; $P<0.001$). We compared the numbers of breast cancers among the 214 high-risk probands with the numbers among their 403 sisters who had not undergone prophylactic mastectomy. Of these sisters, 38.7 percent (156) had been given a diagnosis of breast cancer (115 cases were diagnosed before the respective proband's prophylactic mastectomy, 38 were diagnosed afterward, and the time of the diagnosis was unknown in 3 cases). By contrast, breast cancer was diagnosed in 1.4 percent (3 of 214) of the probands. Thus, prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90 percent.

Conclusions In women with a high risk of breast cancer on the basis of family history, prophylactic mastectomy can significantly reduce the incidence of breast cancer. (N Engl J Med 1999;340:77-84.)

VOLUME 22 · NUMBER 6 · MARCH 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

The Breast Centre

thebreastcentre.com.au

Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group

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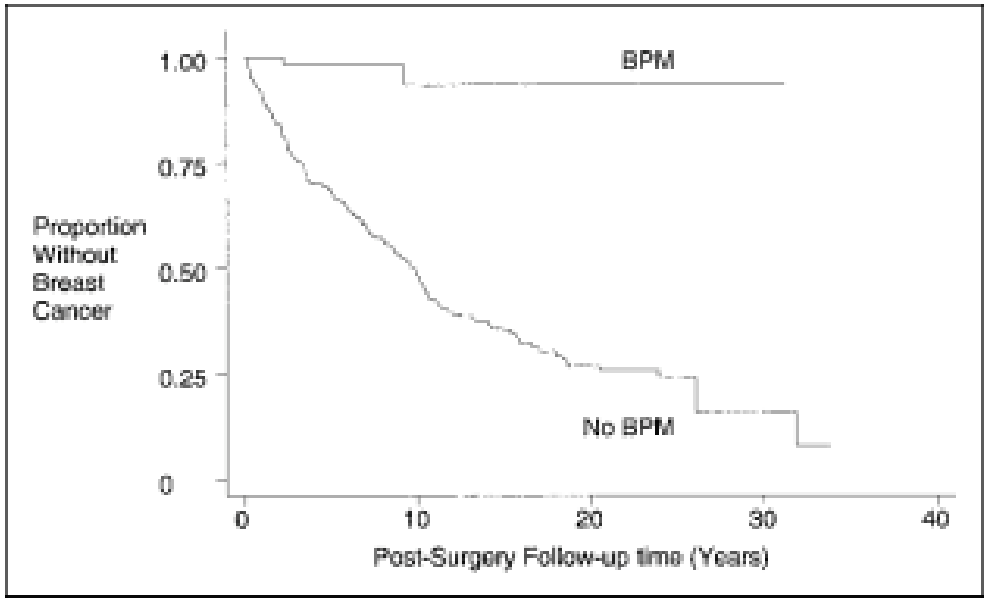

Fig 1. Time to breast cancer diagnosis in female *BRCA1* mutation carriers with and without bilateral prophylactic mastectomy (BPM).

ABSTRACT

Purpose
Data on the efficacy of bilateral prophylactic mastectomy for breast cancer risk reduction in women with *BRCA1* and *BRCA2* (*BRCA1/2*) mutations are limited, despite the clinical use of this risk-management strategy. Thus, we estimated the degree of breast cancer risk reduction after surgery in women who carry these mutations.

Patients and Methods
Four hundred eighty-three women with disease-associated germline *BRCA1/2* mutations were studied for the occurrence of breast cancer. Cases were mutation carriers who underwent bilateral prophylactic mastectomy and who were followed prospectively from the time of their center ascertainment and their surgery, with analyses performed for both follow-up periods. Controls were *BRCA1/2* mutation carriers with no history of bilateral prophylactic mastectomy matched to cases on gene, center, and year of birth. Both cases and controls were excluded for previous or concurrent diagnosis of breast cancer. Analyses were adjusted for duration of endogenous ovarian hormone exposure, including age at bilateral prophylactic oophorectomy if applicable.

Results
Breast cancer was diagnosed in two (1.9%) of 105 women who had bilateral prophylactic mastectomy and in 184 (48.7%) of 378 matched controls who did not have the procedure, with a mean follow-up of 6.4 years. Bilateral prophylactic mastectomy reduced the risk of breast cancer by approximately 95% in women with prior or concurrent bilateral prophylactic oophorectomy and by approximately 90% in women with intact ovaries.

Conclusion
Bilateral prophylactic mastectomy reduces the risk of breast cancer in women with *BRCA1/2* mutations by approximately 90%.

J Clin Oncol 2004 22:1055-1062

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

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Abstract

BACKGROUND: Mutations in *BRCA1* or *BRCA2* genes results in an elevated risk for developing both breast and ovarian cancers over the lifetime of affected carriers. General surgeons may be faced with questions about surgical risk reduction and survival benefit of prophylactic surgery.

METHODS: A systematic literature review was performed using the electronic databases PubMed, OVID MEDLINE, and Scopus comparing prophylactic surgery vs observation with respect to breast and ovarian cancer risk reduction and mortality in *BRCA* mutation carriers.

RESULTS: Bilateral risk-reducing mastectomy provides a 90% to 95% risk reduction in *BRCA* mutation carriers, although the data do not demonstrate improved mortality. The reduction in ovarian and breast cancer risks using risk-reducing bilateral salpingo-oophorectomy has translated to improvement in survival.

CONCLUSIONS: Clinical management of patients at increased risk for breast cancer requires consideration of risk, patient preference, and quality of life.

The American Journal of Surgery, Vol 212, No 4, October 2016

The Breast Centre

thebreastcentre.com.au

Evidence for Oncological Safety of Nipple-Sparing Bilateral Risk-Reduction Mastectomy

ST VINCENT'S PRIVATE HOSPITAL
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Research

JAMA Surgery | Original Investigation

Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in a Population With *BRCA* Mutations

A Multi-institutional Study

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Key Points

Question Is prophylactic nipple-sparing mastectomy oncologically safe for patients with *BRCA* mutations?

Findings This review included a cohort of 346 patients from 9 institutions who underwent 548 risk-reducing nipple-sparing mastectomies. At a median and mean follow-up of 34 and 56 months, respectively, no breast cancers developed.

Meaning Nipple-sparing mastectomy is a highly effective breast cancer prevention strategy in patients with *BRCA* mutations, and nipple-sparing mastectomy should be offered as a risk-reducing approach.

IMPORTANCE Nipple-sparing mastectomy (NSM) offers superior cosmetic outcomes and has been gaining wide acceptance; however, its role among patients with *BRCA* mutations remains controversial.

OBJECTIVE To report on the oncologic safety of NSM and provide evidence-based data to patients and health care professionals regarding preservation of the nipple-areolar complex during a risk-reducing mastectomy in a population with *BRCA* mutations.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively reviewed the outcomes of 9 institutions' experience with prophylactic NSM from 1968 to 2013 in a cohort of patients with *BRCA* mutations. Patients with breast cancer were included if they underwent contralateral risk-reducing mastectomy; however, only the prophylactic side was considered in the analysis. Patients found to have an occult primary breast cancer at the time of risk-reducing mastectomy, those having variant(s) of unknown significance, and those undergoing free nipple grafts were excluded.

MAIN OUTCOMES AND MEASURES The primary outcome measure was development of a new breast cancer after risk-reducing NSM. Three reference data sources were used to model the expected number of events, and this was compared with our observed number of events.

RESULTS A total of 548 risk-reducing NSMs in 346 patients were performed at 9 institutions. The median age at NSM was 41 years (interquartile range, 34.5-47.5 years). Bilateral prophylactic NSMs were performed in 202 patients (58.4%), and 144 patients (41.6%) underwent a unilateral risk-reducing NSM secondary to cancer in the contralateral breast. Overall, 201 patients with *BRCA1* mutations and 145 with *BRCA2* mutations were included. With median and mean follow-up of 34 and 56 months, respectively, no ipsilateral breast cancers occurred after prophylactic NSM. Breast cancer did not develop in any patients undergoing bilateral risk-reducing NSMs. Using risk models for *BRCA1/2* mutation carriers, approximately 22 new primary breast cancers were expected without prophylactic NSM. Prophylactic NSM resulted in a significant reduction in breast cancer events (test of observed vs expected events, $P < .001$).

CONCLUSIONS AND RELEVANCE Nipple-sparing mastectomies are highly preventive against breast cancer in a *BRCA* population. Although the follow-up remains relatively short, NSM should be offered as a breast cancer risk-reducing strategy to appropriate patients with *BRCA* mutations.

JAMA Surg. 2018;153(2):123-129

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Evolving indications and long-term oncological outcomes of risk-reducing bilateral nipple-sparing mastectomy

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Background: Bilateral nipple-sparing mastectomy (NSM) is a technically feasible operation and is associated with excellent cosmetic outcomes. The aim of this study was to evaluate trends in patient characteristics, indications for surgery and long-term outcomes of bilateral NSM for breast cancer risk reduction over time.

Methods: A review of a single-centre experience with bilateral NSM performed between 2001 and 2017 for breast cancer risk reduction in patients without breast cancer was performed. Trends in patient characteristics and indications for surgery were evaluated over four time intervals: 2001–2005, 2006–2009, 2010–2013 and 2014–2017. Statistical analysis was performed using χ^2 tests.

Results: Over the study period, 272 NSMs were performed in 136 patients; their median age was 41 years. The number of bilateral NSMs performed increased over time. The most common indication was a mutation in breast cancer-associated genes (104 patients, 76·5 per cent), which included *BRCA1* (62 patients), *BRCA2* (35), *PTEN* (2), *TP53* (3) and *ATM* (2). Other indications were family history of breast cancer (19 patients, 14·0 per cent), lobular carcinoma *in situ* (10, 7·4 per cent) and a history of mantle irradiation (3, 2·2 per cent). The proportion of patients having a bilateral NSM for mutation in a breast cancer-associated gene increased over time (2001–2005: 2 of 12; 2006–2009: 9 of 17; 2010–2013: 34 of 41; 2014–2017: 61 of 66; $P < 0·001$). Mean follow-up was 53 months; no breast cancers were found during follow-up.

Conclusion: The use of bilateral NSM for breast cancer risk reduction is increasing and the indications have evolved over the past 16 years. These excellent long-term oncological results suggest that bilateral NSM is a good option for surgical breast cancer risk reduction.

BJS Open 2019; 3: 169–173

How Protective are Nipple-Sparing Prophylactic Mastectomies in BRCA1 and BRCA2 Mutation Carriers?

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ABSTRACT

Background. Nipple-sparing mastectomy (NSM) is now routinely offered to BRCA mutation carriers for risk reduction. We assessed the rates of ipsilateral cancer events after prophylactic and therapeutic NSM in BRCA1 and BRCA2 mutation carriers.

Methods. BRCA1 and BRCA2 mutation carriers undergoing NSM from October 2007 to June 2019 were identified in a single-institution prospective database, with variants of unknown significance being excluded. Patient, tumor, and outcomes data were collected. Follow-up analysis was by cumulative breast-years (total years of follow-up of each breast) and woman-years (total years of follow-up of each woman).

Results. Overall, 307 BRCA1 and BRCA2 mutation carriers (160 BRCA1, mean age 41.4 years [range 21–65]; and 147 BRCA2, mean age 43.8 years [range 23–65]) underwent 607 NSMs, with a median follow-up of 42 months (range 1–143). 388 bilateral prophylactic NSMs had 744 cumulative woman-years of follow-up, with no new cancers seen (< 0.0013 new cancers per woman-years); 251 BRCA1 prophylactic NSMs had 1034 cumulative breast-years of follow-up, with no new ipsilateral cancers seen (< 0.0010 per breast-year); 66 BRCA1 therapeutic NSMs had 328 cumulative breast-years of follow-up, with one ipsilateral cancer recurrence not directly involving the nipple or areola (0.0030 per breast-year); 237 BRCA2 prophylactic NSMs had 926 cumulative breast-years of follow-up, with no new ipsilateral cancers seen (< 0.0011 per breast-year); and 53 BRCA2 therapeutic NSMs had 239 cumulative breast-years of follow-up, with two ipsilateral recurrent cancers, neither of which directly involved the nipple or areola (0.0084 per breast-year).

Conclusions. The risk of new ipsilateral breast cancers is extremely low after NSM in BRCA1 and BRCA2 mutation carriers. NSM is an effective risk-reducing strategy for BRCA gene mutations.

TABLE 2 Risk of developing breast cancer after bilateral prophylactic NSM in BRCA1 and BRCA2 mutation carriers, by woman-years of follow-up

	BRCA1 carriers [$n = 160$]	BRCA2 carriers [$n = 147$]	All BRCA1 and BRCA2 carriers [$N = 307$]
Bilateral NSMs (no. of breasts)	198	190	388
Follow-up, months [median (range)]	48 (1–118)	34 (1–143)	38 (1–143)
Cumulative woman-years of follow-up	383	361	744
Annual rate of new cancers (prophylactic, per breast)	< 0.0026/year	< 0.0028/year	< 0.0013/year

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Evidence for Survival Benefit in BRCA Carriers associated with

* Enhanced Screening
* Risk-Reduction Surgery

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JAMA Oncology | Original Investigation

MRI Surveillance and Breast Cancer Mortality in Women With *BRCA1* and *BRCA2* Sequence Variations

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Key Points

Question What is the breast cancer mortality risk of women with a *BRCA1* or *BRCA2* sequence variation after entering a magnetic resonance imaging (MRI) surveillance program?

Findings This cohort study included 1442 women with *BRCA1* and 314 with *BRCA2* sequence variations who underwent a mean of 4.7 screening MRI examinations. At 20 years, the risk of breast cancer mortality was 3.2% in the MRI surveillance group compared with 14.9% for women who did not undergo MRI surveillance.

Meaning Results of this study suggest that among women with a *BRCA1* sequence variation, MRI surveillance is associated with reduced breast cancer mortality risk.

IMPORTANCE Magnetic resonance imaging (MRI) surveillance is offered to women with a pathogenic variant in the *BRCA1* or *BRCA2* gene who face a high lifetime risk of breast cancer. Surveillance with MRI is effective in downstaging breast cancers, but the association of MRI surveillance with mortality risk has not been well defined.

OBJECTIVE To compare breast cancer mortality rates in women with a *BRCA1* or *BRCA2* sequence variation who entered an MRI surveillance program with those who did not.

DESIGN, SETTING, AND PARTICIPANTS Women with a *BRCA1* or *BRCA2* sequence variation were identified from 59 participating centers in 11 countries. Participants completed a baseline questionnaire between 1995 and 2015 and a follow-up questionnaire every 2 years to document screening histories, incident cancers, and vital status. Women who had breast cancer, a screening MRI examination, or bilateral mastectomy prior to enrollment were excluded. Participants were followed up from age 30 years (or the date of the baseline questionnaire, whichever was later) until age 75 years, the last follow-up, or death from breast cancer. Data were analyzed from January 1 to July 31, 2023.

EXPOSURES Entrance into an MRI surveillance program.

MAIN OUTCOMES AND MEASURES Cox proportional hazards modeling was used to estimate the hazard ratios (HRs) and 95% CIs for breast cancer mortality associated with MRI surveillance compared with no MRI surveillance using a time-dependent analysis.

RESULTS A total of 2488 women (mean [range] age at study entry 41.2 [30-69] years), with a sequence variation in the *BRCA1* (n = 2004) or *BRCA2* (n = 484) genes were included in the analysis. Of these participants, 1756 (70.6%) had at least 1 screening MRI examination and 732 women (29.4%) did not. After a mean follow-up of 9.2 years, 344 women (13.8%) developed breast cancer and 35 women (1.4%) died of breast cancer. The age-adjusted HRs for breast cancer mortality associated with entering an MRI surveillance program were 0.20 (95% CI, 0.10-0.43; $P < .001$) for women with *BRCA1* sequence variations and 0.87 (95% CI, 0.10-17.25; $P = .93$) for women with *BRCA2* sequence variations.

CONCLUSION AND RELEVANCE Results of this cohort study suggest that among women with a *BRCA1* sequence variation, MRI surveillance was associated with a significant reduction in breast cancer mortality compared with no MRI surveillance. Further studies of women with *BRCA2* sequence variations are needed to ascertain these women obtain the same benefits associated with MRI surveillance.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival Analysis of Cancer Risk Reduction Strategies for *BRCA1/2* Mutation Carriers

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See accompanying editorial on page 189

A B S T R A C T

Purpose

Women with *BRCA1/2* mutations inherit high risks of breast and ovarian cancer; options to reduce cancer mortality include prophylactic surgery or breast screening, but their efficacy has never been empirically compared. We used decision analysis to simulate risk-reducing strategies in *BRCA1/2* mutation carriers and to compare resulting survival probability and causes of death.

Methods

We developed a Monte Carlo model of breast screening with annual mammography plus magnetic resonance imaging (MRI) from ages 25 to 69 years, prophylactic mastectomy (PM) at various ages, and/or prophylactic oophorectomy (PO) at ages 40 or 50 years in 25-year-old *BRCA1/2* mutation carriers.

Results

With no intervention, survival probability by age 70 is 53% for *BRCA1* and 71% for *BRCA2* mutation carriers. The most effective single intervention for *BRCA1* mutation carriers is PO at age 40, yielding a 15% absolute survival gain; for *BRCA2* mutation carriers, the most effective single intervention is PM, yielding a 7% survival gain if performed at age 40 years. The combination of PM and PO at age 40 improves survival more than any single intervention, yielding 24% survival gain for *BRCA1* and 11% for *BRCA2* mutation carriers. PM at age 25 instead of age 40 offers minimal incremental benefit (1% to 2%); substituting screening for PM yields a similarly minimal decrement in survival (2% to 3%).

Conclusion

Although PM at age 25 plus PO at age 40 years maximizes survival probability, substituting mammography plus MRI screening for PM seems to offer comparable survival. These results may guide women with *BRCA1/2* mutations in their choices between prophylactic surgery and breast screening.

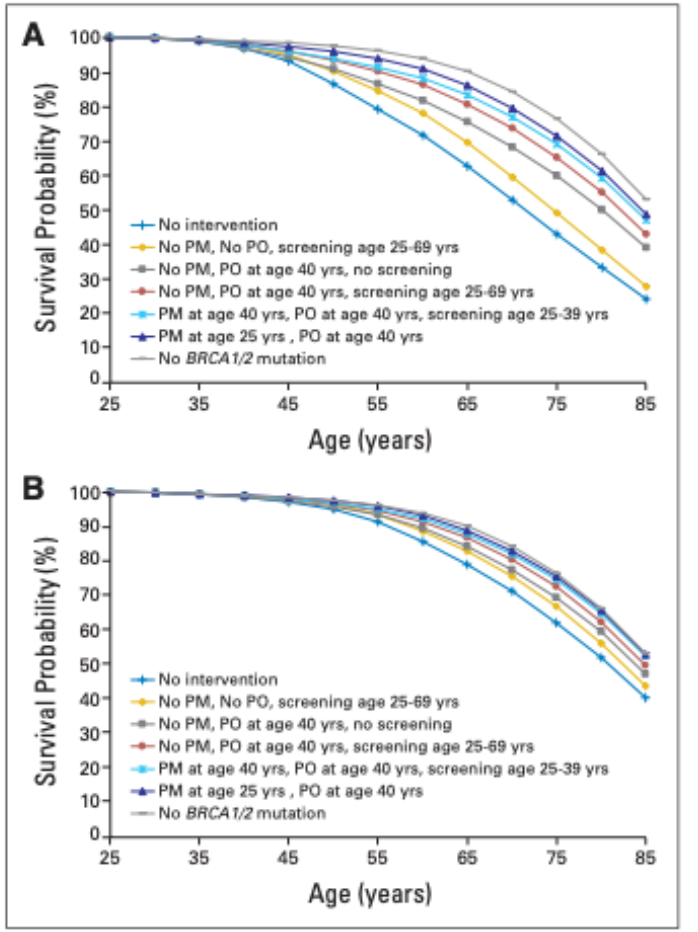

Fig 1. Survival probability after different risk-reducing strategies, including no intervention, screening with mammography plus magnetic resonance imaging (screening), prophylactic mastectomy (PM), and prophylactic oophorectomy (PO) performed at various ages in 25-year-old women with mutations in (A) *BRCA1* and (B) *BRCA2*, compared with women without *BRCA1/2* mutations.

J Clin Oncol 2009 28:222-231.

EPIDEMIOLOGY

Survival after bilateral risk-reducing mastectomy in healthy *BRCA1* and *BRCA2* mutation carriers

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Abstract

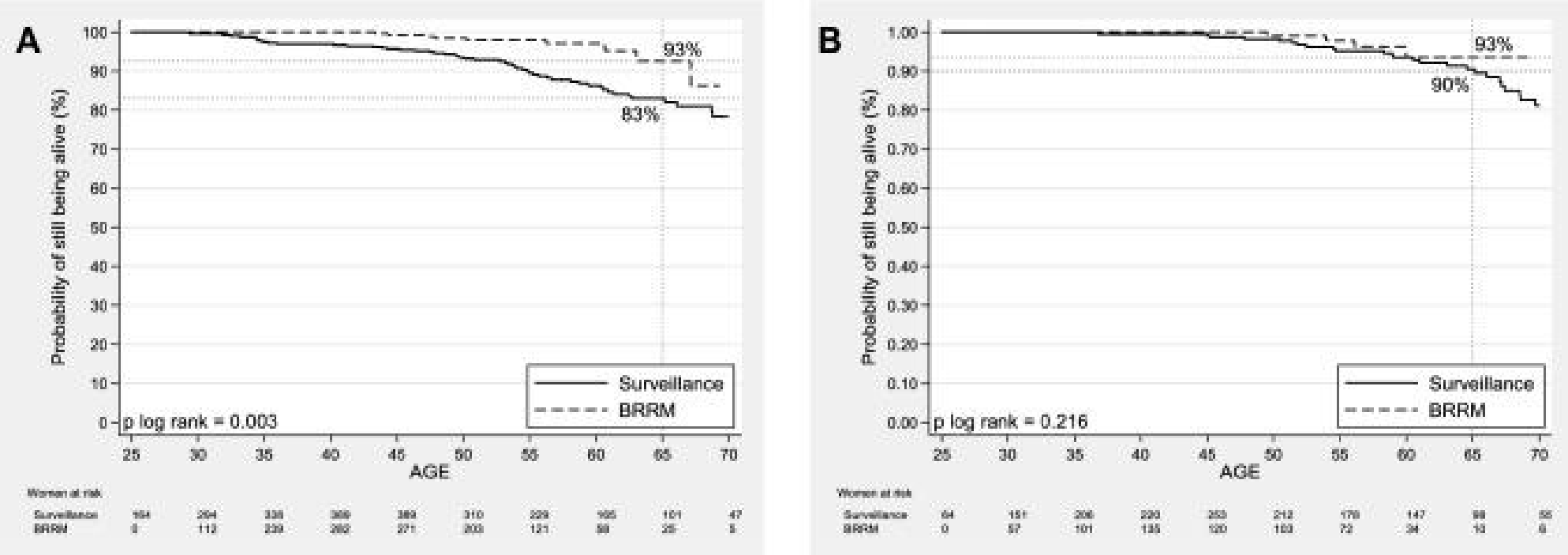
Background In healthy *BRCA1/2* mutation carriers, bilateral risk-reducing mastectomy (BRRM) strongly reduces the risk of developing breast cancer (BC); however, no clear survival benefit of BRRM over BC surveillance has been reported yet.

Methods In this Dutch multicenter cohort study, we used multivariable Cox models with BRRM as a time-dependent covariable to estimate the associations between BRRM and the overall and BC-specific mortality rates, separately for *BRCA1* and *BRCA2* mutation carriers.

Results During a mean follow-up of 10.3 years, 722 out of 1712 *BRCA1* (42%) and 406 out of 1145 *BRCA2* (35%) mutation carriers underwent BRRM. For *BRCA1* mutation carriers, we observed 52 deaths (20 from BC) in the surveillance group, and 10 deaths (one from BC) after BRRM. The hazard ratios were 0.40 (95% CI 0.20–0.90) for overall mortality and 0.06 (95% CI 0.01–0.46) for BC-specific mortality. BC-specific survival at age 65 was 93% for surveillance and 99.7% for BRRM. For *BRCA2* mutation carriers, we observed 29 deaths (7 from BC) in the surveillance group, and 4 deaths (no BC) after BRRM. The hazard ratio for overall mortality was 0.45 (95% CI 0.15–1.36). BC-specific survival at age 65 was 98% for surveillance and 100% for BRRM.

Conclusion BRRM was associated with lower mortality than surveillance for *BRCA1* mutation carriers, but for *BRCA2* mutation carriers, BRRM may lead to similar BC-specific survival as surveillance. Our findings support a more individualized counseling based on BRCA mutation type.

Breast Cancer Research and Treatment (2019) 177:723–733



Overall survival curves for BRCA1 (A) and BRCA2 (B) mutation carriers

Conclusion BRRM was associated with lower mortality than surveillance for *BRCA1* mutation carriers, but for *BRCA2* mutation carriers, BRRM may lead to similar BC-specific survival as surveillance. Our findings support a more individualized counseling based on BRCA mutation type.

Breast Cancer Research and Treatment (2020) 179:251–252
https://doi.org/10.1007/s10549-019-05440-4

LETTER TO THE EDITOR

Risk-reducing mastectomy in BRCA carriers: survival is not the issue

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Familial Cancer (2019) 18:377–379
https://doi.org/10.1007/s10689-019-00142-8

EDITORIAL

Should unaffected female *BRCA2* pathogenic variant carriers be told there is little or no advantage from risk reducing mastectomy?

D. Gareth Evans[1,2,3,4] · Sacha J. Howell[3,4,5] · Anthony Howell[3,4,5]

Breast Cancer Research and Treatment (2020) 179:253–254
https://doi.org/10.1007/s10549-019-05487-3

REBUTTAL LETTER

Risk-reducing mastectomy in BRCA mutation carriers: survival is one of the issues—author's reply

Bernadette Anna Maria Heemskerk-Gerritsen[1] · Maartje Joanneke Hooning[1]

British Journal of Cancer www.nature.com/bjc

ARTICLE

Epidemiology

Risk-reducing mastectomy and breast cancer mortality in women with a *BRCA1* or *BRCA2* pathogenic variant: an international analysis

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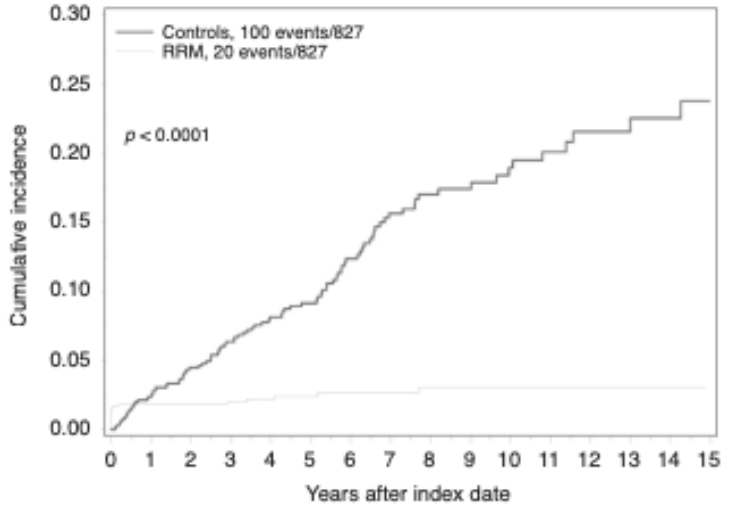

Fig. 1 Breast Cancer Incidence. Cumulative incidence of breast cancer from index date for RRM versus Control.

BACKGROUND: Risk-reducing mastectomy (RRM) is offered to women with a *BRCA1* or *BRCA2* pathogenic variant, however, there are limited data on the impact on breast cancer mortality.

METHODS: Participants were identified from a registry of women with *BRCA1/2* pathogenic variants. We used a pseudo-randomised trial design and matched one woman with a RRM to one woman without a RRM on year of birth, gene, and country. We estimated the hazard ratio (HR) and 95% confidence intervals (CI) for dying of breast cancer in the follow-up period.

RESULTS: There were 1654 women included; 827 assigned to the RRM arm and 827 assigned to the control arm. After a mean follow-up of 6.3 years, there were 20 incident breast cancers (including 15 occult cancers) and two breast cancer deaths in the RRM arm, and 100 incident breast cancers and 7 breast cancer deaths in the control arm (HR = 0.26; 95% CI 0.05–1.35; $p = 0.11$). The probability of dying of breast cancer within 15 years after RRM was 0.95%.

CONCLUSIONS: In women with a *BRCA1* or *BRCA2* pathogenic variant, RRM reduces the risk of breast cancer, and the probability of dying of breast cancer is low.

British Journal of Cancer (2024) 130:269 – 274

ARTICLE

Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction

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Abstract

Background: Previous studies have reported a breast cancer (BC) risk reduction of approximately 50% after risk-reducing salpingo-oophorectomy (RRSO) in BRCA1/2 mutation carriers, but may have been subject to several types of bias. The purpose of this nationwide cohort study was to assess potential bias in the estimated BC risk reduction after RRSO.

Methods: We selected BRCA1/2 mutation carriers from an ongoing nationwide cohort study on Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON). First, we replicated the analytical methods as previously applied in four major studies on BC risk after RRSO. Cox proportional hazards models were used to calculate hazard ratios and conditional logistic regression to calculate odds ratios. Secondly, we analyzed the data in a revised design in order to further minimize bias using an extended Cox model with RRSO as a time-dependent variable to calculate the hazard ratio. The most important differences between our approach and those of previous studies were the requirement of no history of cancer at the date of DNA diagnosis and the inclusion of person-time preceding RRSO.

Results: Applying the four previously described analytical methods and the data of 551 to 934 BRCA1/2 mutation carriers with a median follow-up of 2.7 to 4.6 years, the odds ratio was 0.61 (95% confidence interval [CI] = 0.35 to 1.08), and the hazard ratios were 0.36 (95% CI = 0.25 to 0.53), 0.62 (95% CI = 0.39 to 0.99), and 0.49 (95% CI = 0.33 to 0.71), being similar to earlier findings. For the revised analysis, we included 822 BRCA1/2 mutation carriers. After a median follow-up period of 3.2 years, we obtained a hazard ratio of 1.09 (95% CI = 0.67 to 1.77).

Conclusion: In previous studies, BC risk reduction after RRSO in BRCA1/2 mutation carriers may have been overestimated because of bias. Using a design that maximally eliminated bias, we found no evidence for a protective effect.

JNCI J Natl Cancer Inst, 2015, Vol. 107, No. 5

Risk-Reducing Oophorectomy and Breast Cancer Risk Across the Spectrum of Familial Risk

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Abstract

There remains debate about whether risk-reducing salpingo-oophorectomy (RRSO), which reduces ovarian cancer risk, also reduces breast cancer risk. We examined the association between RRSO and breast cancer risk using a prospective cohort of 17 917 women unaffected with breast cancer at baseline (7.2% known carriers of *BRCA1* or *BRCA2* mutations). During a median follow-up of 10.7 years, 1046 women were diagnosed with incident breast cancer. Modeling RRSO as a time-varying exposure, there was no association with breast cancer risk overall (hazard ratio [HR] = 1.04, 95% confidence interval [CI] = 0.87 to 1.24) or by tertiles of predicted absolute risk based on family history (HR = 0.68, 95% CI = 0.32 to 1.47, HR = 0.94, 95% CI = 0.70 to 1.26, and HR = 1.10, 95% CI = 0.88 to 1.39, for lowest, middle, and highest tertile of risk, respectively) or for *BRCA1* and *BRCA2* mutation carriers when examined separately. There was also no association after accounting for hormone therapy use after RRSO. These findings suggest that RRSO should not be considered efficacious for reducing breast cancer risk.

JNCI J Natl Cancer Inst (2019)

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International trends in the uptake of cancer risk reduction strategies in women with a *BRCA1* or *BRCA2* mutation

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BACKGROUND: Women with a *BRCA1* or *BRCA2* mutation face high risks of breast and ovarian cancer. In the current study, we report on uptake of cancer screening and risk-reduction options in a cohort of *BRCA* mutation carriers from ten countries over two time periods (1995 to 2008 and 2009 to 2017).

METHODS: Eligible subjects were identified from an international database of female *BRCA* mutation carriers and included women from 59 centres from ten countries. Subjects completed a questionnaire at the time of genetic testing, which included past use of cancer prevention options and screening tests. Biennial follow-up questionnaires were administered.

RESULTS: Six-thousand two-hundred and twenty-three women were followed for a mean of 7.5 years. The mean age at last follow-up was 52.1 years (27–96 years) and 42.3% of the women had a prior diagnosis of breast cancer. In all, 27.8% had a prophylactic bilateral mastectomy and 64.7% had a BSO. Screening with breast MRI increased from 70% before 2009 to 81% at or after 2009. There were significant differences in uptake of all options by country.

CONCLUSION: For women who received genetic testing more recently, uptake of prophylactic mastectomy and breast MRI is significantly higher than those who received genetic testing more than 10 years ago. However, uptake of both BSO and breast MRI is not optimal, and interventions to increase uptake are needed.

British Journal of Cancer (2019) 121:15–21

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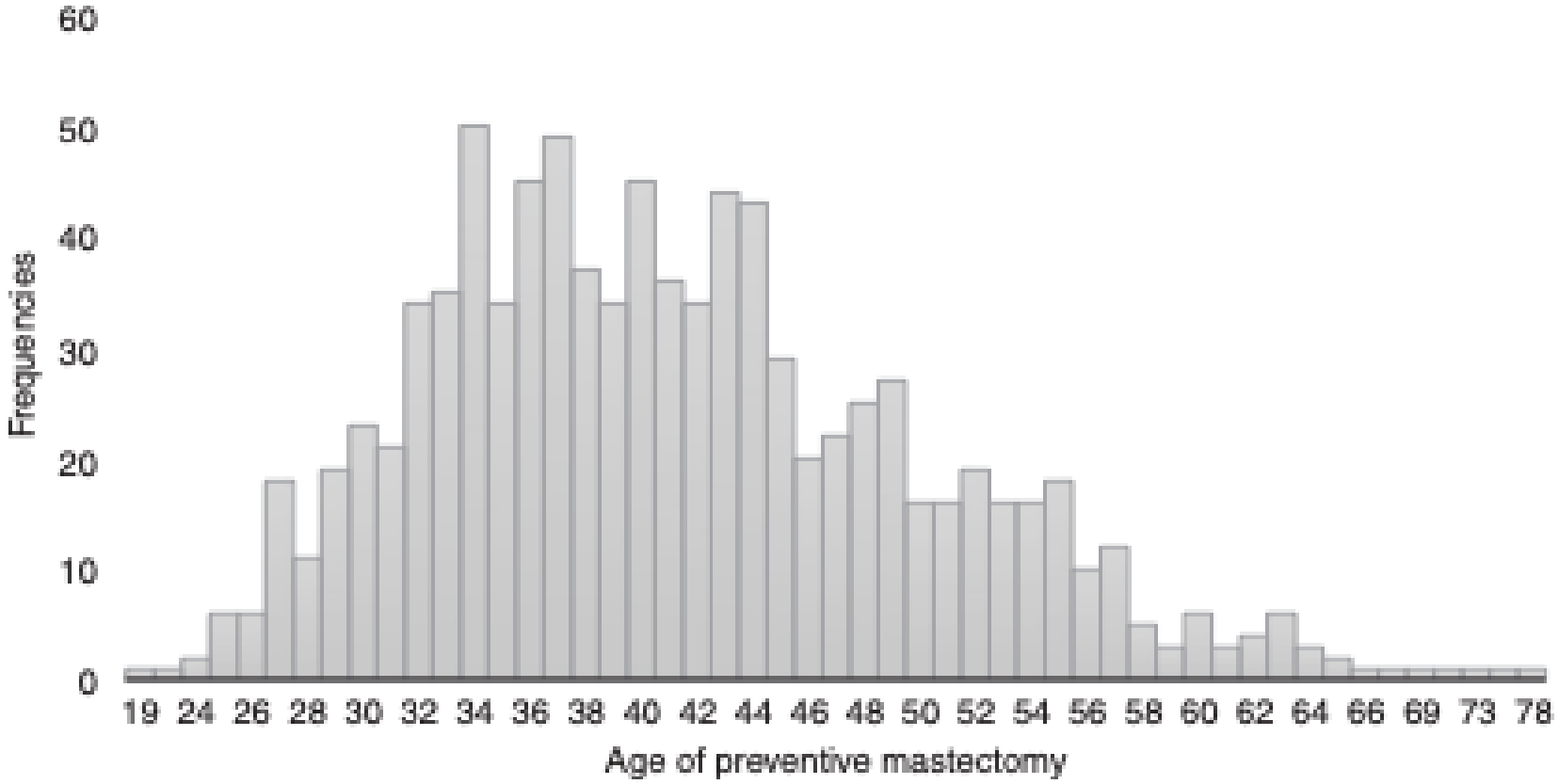

The distribution of age of preventive mastectomy among subjects without breast cancer

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Surgery for BRCA Associated Breast Cancer

Safety of Breast Conserving Therapy (BCT)
vs
Unilateral Mastectomy +/- Contralateral Risk-Reduction Mastectomy (CRRM)

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CLINICAL TRIAL

Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy

Lori J. Pierce · Kelly-Anne Phillips · Kent A. Griffith · Saundra Buys · David K. Gaffney · Meena S. Moran · Bruce G. Haffty · Merav Ben-David · Bella Kaufman · Judy E. Garber · Sofia D. Merajver · Judith Balmaña · Amichay Meirovitz · Susan M. Domchek

Abstract Women with BRCA1 and BRCA2 mutations have an elevated risk of breast cancer and ovarian cancer, but also of developing second primary breast cancer. BRCA1/2 mutation carriers with breast cancer must choose between breast conservation (BCT) and mastectomy (M) yet data on outcomes are limited. The purpose of this study is to compare long-term outcome following BCT and M in BRCA1/2 carriers. 655 women with BRCA1/2 mutations diagnosed with breast cancer and treated with BCT ($n = 302$) or M ($n = 353$) were identified and underwent follow-up to assess local, regional, and systemic recurrence. Local failure as first failure was significantly more likely in those treated with BCT compared to M, with a cumulative estimated risk of 23.5 vs. 5.5%, respectively, at 15 years ($P < 0.0001$); 15-year estimates in carriers treated with BCT and chemotherapy was 11.9% ($P = 0.08$ when compared to M). Most events appeared to be second primary cancers rather than failure to control the primary tumor. The risk of contralateral breast cancer was high in all groups, exceeding 40%, but was not statistically significantly different by use of adjuvant radiotherapy (RT) or not, suggesting no added risk from scatter RT at 10 and 15 years. There were no differences seen in regional or systemic recurrences between the BCT and M groups, and no difference in overall survival. In conclusion, BRCA1/2 mutation carriers with breast cancer have similar survival whether treated with M or BCT. However, women undergoing BCT have an elevated risk of a second in-breast event that is significantly reduced in the presence of chemotherapy. Contralateral breast cancer events are very common.

Presented, in part, at the 2010 European Breast Cancer Conference, Barcelona, Spain, March 2010.

Breast Cancer Res Treat (2010) 121:389–398

CLINICAL TRIAL

High risk of in-breast tumor recurrence after *BRCA1/2*-associated breast cancer

Martin P. Nilsson · Linda Hartman · Ulf Kristoffersson · Oskar T. Johannsson · Åke Borg · Karin Henriksson · Elsa Lanke · Håkan Olsson · Niklas Loman

Abstract The purpose of the study was to compare breast-conserving therapy (BCT) and mastectomy (M) in BRCA1/2 mutation carriers. Women with invasive breast cancer and a pathogenic mutation in *BRCA1* or *BRCA2* were included in the study ($n = 162$). Patients treated with BCT ($n = 45$) were compared with patients treated with M ($n = 118$). Endpoints were local recurrence as first recurrence (LR), overall survival (OS), breast cancer death, and distant recurrence. Cumulative incidence was calculated in the presence of competing risks. For calculation of hazard ratios and for multivariable analysis, cause-specific Cox proportional hazards regression was used. Compared to M, BCT was associated with an increased risk of LR in univariable analysis (HR 4.0; 95 % CI 1.6–9.8) and in multivariable analysis adjusting for tumor stage, age, and use of adjuvant chemotherapy (HR 2.9; CI 1.1–7.8). Following M, all local recurrences were seen in the first 5 years after breast cancer diagnosis. Following BCT, the rate of LR continued to be high also after the first 5 years. The cumulative incidence of LR in the BCT group was 15, 25, and 32 % after 5, 10, and 15 years, respectively. There were no significant differences between BCT and M for OS, breast cancer death, or distant recurrence. *BRCA1/2* mutation carriers treated with BCT have a high risk of LR, many of which are new primary breast cancers. This must be thoroughly discussed with the patient and is an example of how rapid treatment-focused genetic testing could influence choice of treatment.

Keywords Hereditary breast cancer · BRCA1/2 · Breast-

Breast Cancer Res Treat (2014) 147:571–578

Prognostic Impact of Breast-Conserving Therapy Versus Mastectomy of *BRCA1/2* Mutation Carriers Compared With Noncarriers in a Consecutive Series of Young Breast Cancer Patients

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Objective: To investigate the effects of different types of surgery on breast cancer prognosis in germline *BRCA1/BRCA2* mutation carriers compared with noncarriers.

Summary of Background Data: Although breast-conserving therapy (breast-conserving surgery followed by radiotherapy) has been associated with more local recurrences than mastectomy, no differences in overall survival have been found in randomized trials performed in the general breast cancer population. Whether breast-conservation can be safely offered to *BRCA1/2* mutation carriers is debatable.

Methods: The study comprised a cohort of women with invasive breast cancer diagnosed <50 years and treated between 1970 and 2003 in 10 Dutch centers. Germline DNA for *BRCA1/2* testing of most-prevalent mutations (covering ~61%) was mainly derived from paraffin-blocks. Survival analyses were performed taking into account competing risks.

Results: In noncarriers (N = 5820), as well as in *BRCA1* (N = 191) and *BRCA2* (N = 70) mutation carriers, approximately half of the patients received breast-conserving therapy. Patients receiving mastectomy followed by radiotherapy had prognostically worse tumor characteristics and more often received systemic therapy. After adjustment for these potential confounders, patients who received breast-conserving therapy had a similar overall survival compared with patients who received mastectomy, both in noncarriers (hazard ratio [HR] = 0.95, confidence interval [CI] = 0.85–1.07, $P = 0.41$) and *BRCA1* mutation carriers (HR = 0.80, CI = 0.42–1.51, $P = 0.50$). Numbers for *BRCA2* were insufficient to draw conclusions. The rate of local recurrences after breast-conserving therapy did not differ between *BRCA1* carriers (10-year risk = 7.3%) and noncarriers (10-year risk = 7.9%).

Conclusion: Our results, together with the available literature, provide reassurance that breast-conserving therapy is a safe local treatment option to offer to *BRCA1* mutation carriers with invasive breast cancer.

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Original Investigation | Oncology

Clinical Outcomes for *BRCA* Pathogenic Variant Carriers With Breast Cancer Undergoing Breast Conservation

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Key Points

Question What are the long-term clinical outcomes of patients with *BRCA*-associated breast cancer who undergo breast-conserving therapy (BCT)?

Findings In this cohort study of 172 women with *BRCA*-associated breast cancer who underwent BCT, participants had above-average risks of ipsilateral and contralateral breast cancer events; however, if surviving to 10 years, most never experienced either event and were bilateral mastectomy free.

Meaning The long-term cancer event risks and the probability of future bilateral mastectomy can help inform patients with *BRCA*-associated breast cancer choosing breast conservation.

Abstract

IMPORTANCE Although most women with *BRCA*-associated breast cancer choose bilateral mastectomy, current guidelines support breast-conserving therapy as an option. As the indications for genetic testing expand and targeted therapies emerge, understanding the outcomes of breast-conserving therapy in the population of patients choosing breast conservation is important.

OBJECTIVE To describe the clinical outcomes of women with *BRCA*-associated breast cancer who were treated with breast-conserving therapy, including the risks of ipsilateral and contralateral cancer events and bilateral mastectomy-free survival.

DESIGN, SETTING, AND PARTICIPANTS This cohort study conducted at a single-institution academic national comprehensive cancer center included 172 women identified from a prospectively maintained database who had pathogenic *BRCA1/2* variants and were treated with breast-conserving therapy from January 1, 1977, to December 31, 2021.

MAIN OUTCOMES AND MEASURES Clinical and pathologic characteristics for patients with *BRCA1* and *BRCA2* were compared, and estimates of overall survival, bilateral mastectomy-free survival, distant disease-free survival, risk of ipsilateral breast cancer, and risk of contralateral cancer were computed.

RESULTS The cohort included 172 women (mean [SD] age, 47.1 [11.7] years), with 42 (24.4%) receiving a diagnosis of breast cancer prior to 40 years of age. Compared with *BRCA2* variant carrie (80 [46.5%]), women with *BRCA1* variants (92 [53.5%]) were younger at breast cancer diagnosis an tended to have more advanced tumors, which were more likely to be hormone receptor negative and higher grade. At a median follow-up of 11.8 years (IQR, 5.7-18.2 years), estimates of 10-year survival and risk were: overall survival, 88.5% (95% CI, 83.1%-94.2%); bilateral mastectomy-free survival, 70.7% (95% CI, 63.3%-78.9%); risk of an ipsilateral breast cancer event, 12.2% (95% CI, 5.8%-18.2%); and risk of contralateral cancer, 21.3% (95% CI, 13.3%-28.6%). Risks continued to increase after 10 years of follow-up.

CONCLUSIONS AND RELEVANCE In this cohort study, although women with breast cancer and pathogenic *BRCA1/2* variants treated with breast-conserving therapy had above-average risks of ipsilateral and contralateral breast cancer events, most did not have another cancer event and remained bilateral mastectomy free. These findings may be useful for informing patients with *BRCA* variants choosing breast conservation.

JAMA Network Open. 2024 June 25, 7(6):e2418486

Review

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Breast Conserving Surgery for BRCA Mutation Carriers—A Systematic Review

Michael Co, Thomas Liu, Jason Leung, Chung Hin Li, Theo Tse, Michael Wong, Ava Kwong

Abstract

Similar to mastectomy, breast conserving surgery (BCS) is currently the reference standard of surgical treatment of sporadic breast cancer in patients. However, its oncologic safety for BRCA mutation carriers has remained controversial. Thus, we conducted a systematic review to critically evaluate the best evidence from reported studies. A comprehensive search was performed of the Medline, EMBASE, CINAHL, and Cochrane databases using a predefined strategy. The retrieved studies were independently screened and rated for relevance. Data were extracted for qualitative synthesis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol for systematic reviews. No randomized controlled trial has directly compared BCS and mastectomy for BRCA mutation carriers. Of the 18 studies included in our review, the pooled analysis of overall survival at 5, 10, and 15 years were comparable between BCS and mastectomy (88.7%, 89.0% and 83.6% with BCS and 83%, 86.0%, and 83.2% with mastectomy, respectively). However, the pooled ipsilateral breast cancer recurrence rates at 5, 10, and 15 years were higher in the BCS group (8.2%, 15.5%, and 23%, respectively) than in the mastectomy group (3.4%, 4.9%, and 6.4%, respectively). BCS was associated with a greater rate of ipsilateral breast cancer recurrence in BRCA mutation carriers. However, it was not associated with adverse short- and long-term survival outcomes. BCS should be offered as an option to BRCA mutation carriers with proper preoperative counseling.

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Table 1 Overall Survival of Breast Conserving Surgery and Mastectomy in BRCA Mutation Carriers

Study	Design	Stage	Overall Survival/Total Patients Who Underwent Surgery					
			5 y		10 y		15 y	
			BCS	M	BCS	M	BCS	M
Robson et al,[19] 2005	Case series	T1-T2	85/87 (95.6)	NA	78/87 (89.4)	NA	NA	NA
Garcia-Etienne et al,[20] 2009	Retrospective cohort	T1-T3	NA	NA	278/302 (92.1)	324/353 (91.8)	264/302 (87.3)	317/353 (89.8)
Nilsson et al,[21] 2014	Prospective cohort	I-III	36/45 (80)	97/117 (83)	31/45 (68)	80/117 (68)	26/45 (58)	74/117 (63)
Pierce et al,[22] 2000	Retrospective cohort	NA	61/71 (86)	NA	NA	NA	NA	NA
Overall pooled	NA	NA	182/203 (89.7)	97/117 (83)	387/434 (89.0)	404/470 (86.0)	290/347 (83.6)	391/470 (83.2)

Table 2 Summary of 5-Year Local Recurrence Rate After BCS and Mastectomy in BRCA Mutation Carriers

Investigator	Design	Patient Characteristics	Recurrence	
			After BCS	After Mastectomy
Pierce et al,[22] 2000	Retrospective cohort	Stage I-II	2/71 (2)	0 (0)
Haffty et al,[23] 2002	Retrospective cohort	Tis-T2 stage	5/22 (22)	0 (0)
Seynaeve et al,[24] 2004	Retrospective cohort	Stage I-IV	12/87 (14)	0 (0)
Robson et al,[19] 2005	Retrospective cohort	T1-T2 stage	11/95 (11.2)	0 (0)
Brekelmans et al,[25] 2007	Retrospective cohort	T1-T4 stage	14/111 (12.6); BRCA2, 5/35 (17); BRCA1, 9/76 (12)	0 (0)
Garcia-Etienne et al,[20] 2009	Retrospective cohort	T1-T3 stage	8/54 (15)	0 (0)
Pierce et al,[16] 2010	Prospective cohort	Stage I-III	12/302 (4.1)	5/353 (1.4)
Kirova et al,[26] 2010	Retrospective cohort	T1-T2 stage	6/29 (21)	0 (0)
Metcalfe et al,[27] 2011	Prospective cohort	Stage I-III	23/396 (5.8)	0 (0)
Nilsson et al,[21] 2014	Prospective cohort	Stage I-III	7/45 (15)	11/117 (9)
Overall	NA	NA	100/1212 (8.2)	16/470 (3.4)

Table 3 Summary of 10-Year Local Recurrence Rate After BCS and Mastectomy in BRCA Mutation Carriers

Study	Design	Patient Characteristics	Recurrence	
			After BCS	After Mastectomy
Eccles et al,[28] 2001	Retrospective cohort	Mean primary tumor size, 2.5 cm	6/36 (16.7)	0 (0)
Haffty et al,[23] 2002	Retrospective cohort	Tis-T2 stage	9/22 (41)	0 (0)
Seynaeve et al,[24] 2004	Retrospective cohort	Stage I-IV	26/87 (30)	0 (0)
Robson et al,[4] 2004	Retrospective cohort	T1-T2 stage	7/56 (12)	0 (0)
Robson et al,[19] 2005	Retrospective cohort	T1-T2 stage	13/95 (13.6)	0 (0)
Pierce et al,[29] 2006	Prospective cohort	T1-T2 stage	19/160 (12)	0 (0)
Brekelmans et al,[25] 2007	Retrospective cohort	T1-T4 stage	18/111 (16.2)	0 (0)
Garcia-Etienne et al,[20] 2009	Retrospective cohort	T1-T3 stage	15/54 (27)	0 (0)
Kirova et al,[26] 2010	Retrospective cohort	T1-T2 stage	15/29 (52)	0 (0)
Pierce et al,[16] 2010	Prospective cohort	Stage I-III	32/302 (10.5)	12/353 (3.5)
Metcalfe et al,[27] 2011	Prospective cohort	Stage I-II	49/396 (12.5)	0 (0)
Nilsson et al,[21] 2014	Prospective cohort	Stage I-III	11/45 (25)	11/117 (9)
Fita et al,[30] 2016	Retrospective cohort	Stage I-III	23/173 (13.3)	0 (0)
Overall	NA	NA	243/1566 (15.5)	23/470 (4.9)

Table 4 Summary of 15-Year Local Recurrence Rate After BCS and Mastectomy in BRCA Mutation Carriers

Investigator	Design	Patient Characteristics	Recurrence	
			After BCS	After Mastectomy
Seynaeve et al,[24] 2004	Retrospective cohort	Stage I-IV	43/87 (49)	0 (0)
Robson et al,[19] 2005	Retrospective cohort	T1-T2 stage	22/95 (23.4)	0 (0)
Pierce et al,[29] 2006	Prospective cohort	T1-T2 stage	38/160 (24)	0 (0)
Pierce et al,[16] 2010	Prospective cohort	Stage I-III	71/302 (23.5)	19/353 (5.5)
Metcalfe et al,[27] 2011	Prospective cohort	Stage I-II	62/396 (15.8)	0 (0)
Nilsson et al,[21] 2014	Prospective cohort	Stage I-III	14/45 (32)	11/117 (9)
Overall	NA	NA	250/1085 (23.0)	30/470 (6.4)

Table 5 Summary of Ipsilateral Local Recurrence Rate of BCS and Mastectomy in BRCA Mutation Carriers

Postoperative Duration, y	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

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Evidence for Increased Contralateral Breast Cancer (CBC) Risk in Carriers of Pathogenic Gene Variants

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original reports

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*

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abstract

PURPOSE To estimate the risk of contralateral breast cancer (CBC) among women with germline pathogenic variants (PVs) in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*.

METHODS The study population included 15,104 prospectively followed women within the CARRIERS study treated with ipsilateral surgery for invasive breast cancer. The risk of CBC was estimated for PV carriers in each gene compared with women without PVs in a multivariate proportional hazard regression analysis accounting for the competing risk of death and adjusting for patient and tumor characteristics. The primary analyses focused on the overall cohort and on women from the general population. Secondary analyses examined associations by race/ethnicity, age at primary breast cancer diagnosis, menopausal status, and tumor estrogen receptor (ER) status.

RESULTS Germline *BRCA1*, *BRCA2*, and *CHEK2* PV carriers with breast cancer were at significantly elevated risk (hazard ratio > 1.9) of CBC, whereas only the *PALB2* PV carriers with ER-negative breast cancer had elevated risks (hazard ratio, 2.9). By contrast, *ATM* PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Among premenopausal women, the 10-year cumulative incidence of CBC was estimated to be 33% for *BRCA1*, 27% for *BRCA2*, and 13% for *CHEK2* PV carriers with breast cancer and 35% for *PALB2* PV carriers with ER-negative breast cancer. The 10-year cumulative incidence of CBC among postmenopausal PV carriers was 12% for *BRCA1*, 9% for *BRCA2*, and 4% for *CHEK2*.

CONCLUSION Women diagnosed with breast cancer and known to carry germline PVs in *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2* are at substantially increased risk of CBC and may benefit from enhanced surveillance and risk reduction strategies.

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CONTEXT

Key Objective

To estimate the risk of contralateral breast cancer (CBC) in carriers of germline pathogenic variants (PVs) in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* from prospective studies.

Knowledge Generated

Germline *BRCA1*, *BRCA2*, and *CHEK2* PV carriers with breast cancer were at a significantly elevated risk of CBC, whereas only the *PALB2* PV carriers with estrogen receptor–negative breast cancer had elevated risks. By contrast, *ATM* PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Age at diagnosis, menopausal status, and estrogen receptor status of the initial breast cancer significantly influenced the CBC risk in PV carriers.

Relevance *(K.D. Miller)*

Patients with genetic mutations who have had an index breast cancer often assume that they are at high risk of developing another cancer in the other breast. The ability to better predict risk can guide decisions about prophylactic surgery and enhanced screening strategies for those who opt against bilateral mastectomy.*

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Evidence for Survival Benefit of Contralateral Risk-Reduction Mastectomy (CRRM) in BRCA Carriers

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

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Data on survival of BRCA1/2-associated primary breast cancer (PBC) patients who opt for subsequent contralateral risk-reducing mastectomy (CRRM) are scarce and inconsistent. We examined the efficacy of CRRM on overall survival in mutation carriers with a history of PBC. From a Dutch multicentre cohort, we selected 583 BRCA-associated PBC patients, being diagnosed between 1980 and 2011. Over time, 242 patients (42%) underwent CRRM and 341 patients (58%) remained under surveillance. Survival analyses were performed using Cox models, with CRRM as a time-dependent covariate. The median follow-up after PBC diagnosis was 11.4 years. In the CRRM group, four patients developed contralateral breast cancer (2%), against 64 patients (19%) in the surveillance group ($p < 0.001$). The mortality was lower in the CRRM group than in the surveillance group (9.6 and 21.6 per 1000 person-years of observation, respectively; adjusted hazard ratio 0.49, 95% confidence interval 0.29–0.82). Survival benefit was especially seen in young PBC patients (<40 years), in patients having a PBC with differentiation grade 1/2 and/or no triple-negative phenotype, and in patients not treated with adjuvant chemotherapy.

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