# Risk-reducing mastectomy in women with pathogenic BRCA variations

## Effect on risk of breast cancer, mortality and quality of life

# PhD Thesis

## Risk-reducing mastectomy and immediate breast reconstruction

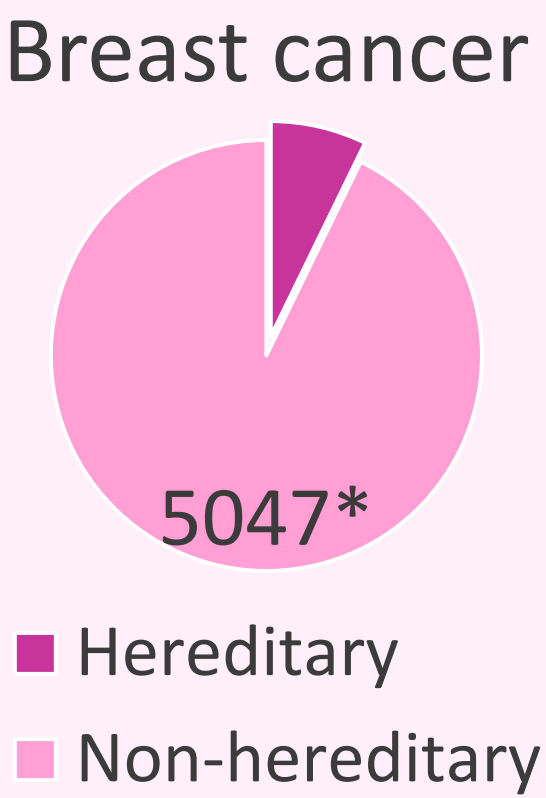
### Psychological and oncological perspectives

June 26, 2025

# Agenda

- Background
- Oncological aspects
- Psychological aspects

# Hereditary breast cancer

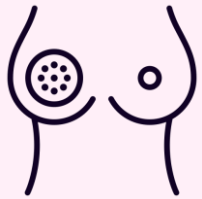



5–10% Hereditary

3% *BRCA1/2*

* *Nordcan (2022)*

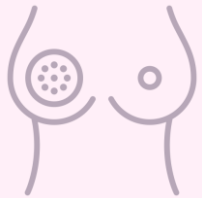
# Pathological variants in the *BRCA1* and *BRCA2* gene increases risk of breast and ovarian cancer

| | *BRCA1* | *BRCA2* | Background |
|---|---|---|---|
|  | 72% | 69% | 13% |
|  | 44% | 17% | 1% |

www.flaticon.com

*Kuchenbaecker (2017 ) and Nordcan (2022)*

# Pathological variants in the *BRCA1* and *BRCA2* gene increases risk of breast and ovarian cancer

| | *BRCA1* | *BRCA2* | Background |
|---|---|---|---|
|  | 72% | | 13% |
|  | 44% | 17% | 1% |

The penetrans varies

Genotype versus fænotype

www.flaticon.com

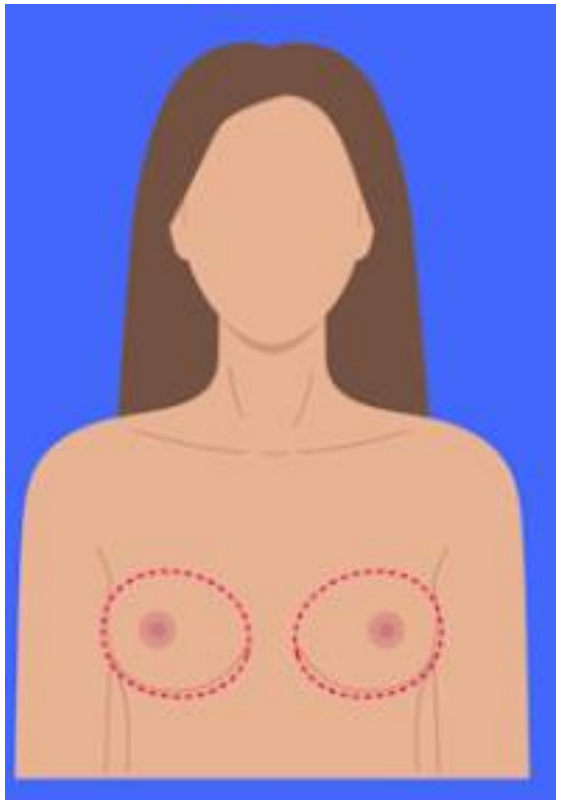
*Kuchenbaecker (2017 ) and Nordcan (2022)*

# Pathogenic variants class 1–5

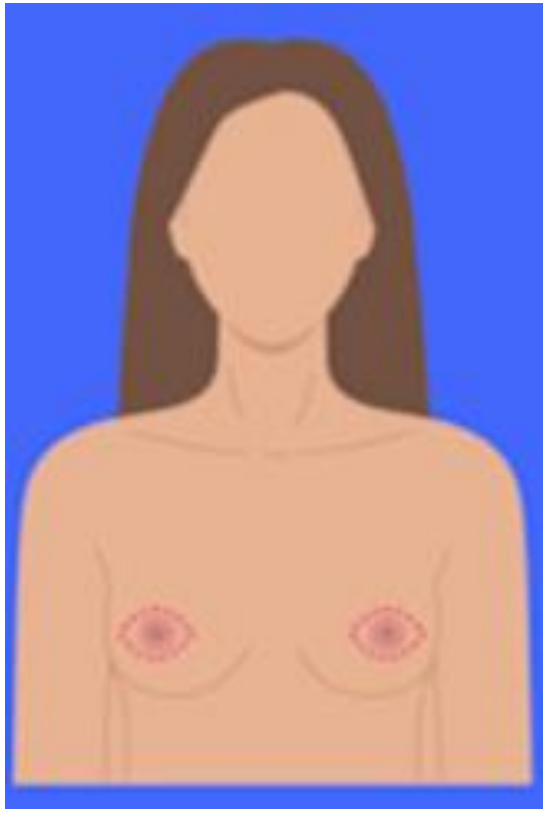
| Class | Pathogenicity |
|---|---|
| 1 | Benign |
| 2 | Likely benign |
| 3 | Uncertain (VUS*) |
| 4 | Likely pathogenic |
| 5 | Pathogenic |

*Variant of uncertain significance

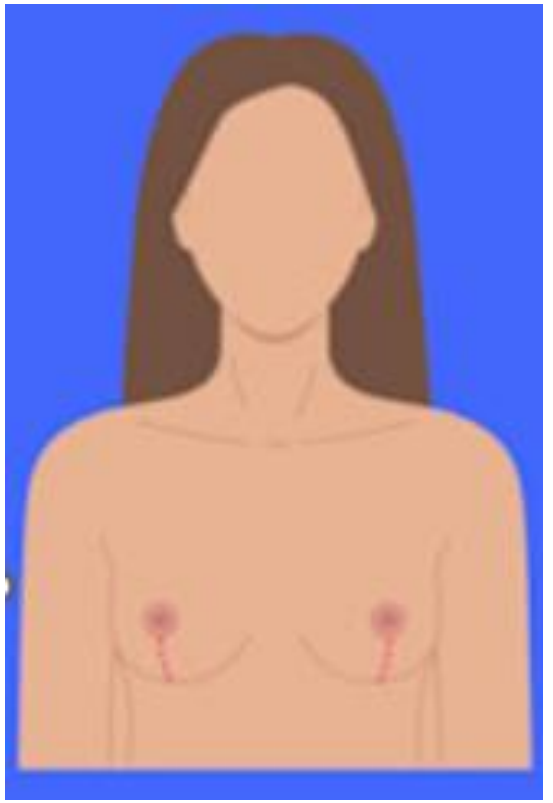
# Bilateral risk-reducing mastectomy



Total mastectomy

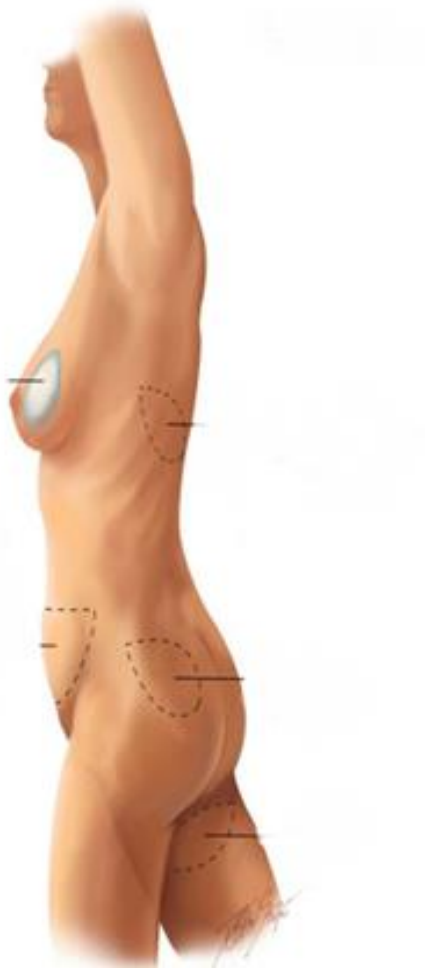


Skin-sparing mastectomy

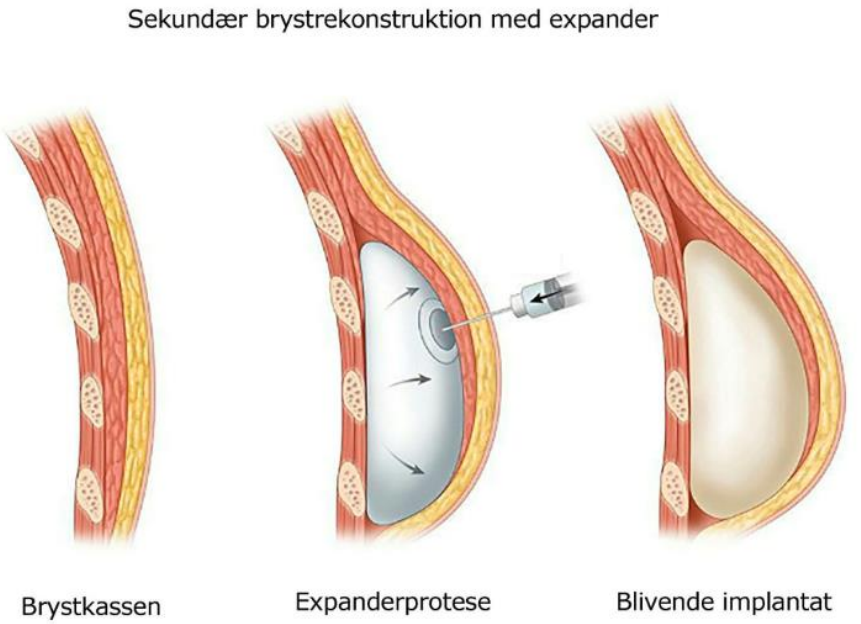


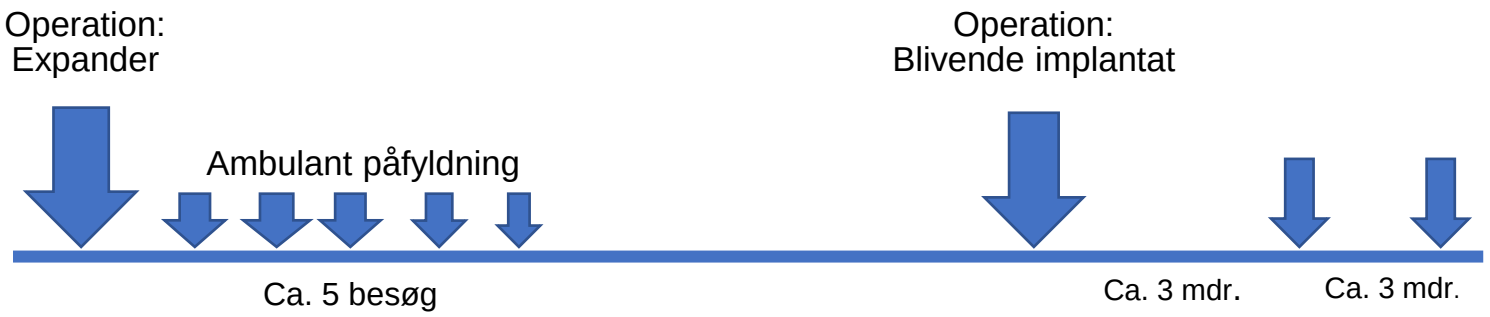
Nipple-sparing mastectomy

# … and immediate breast reconstruction



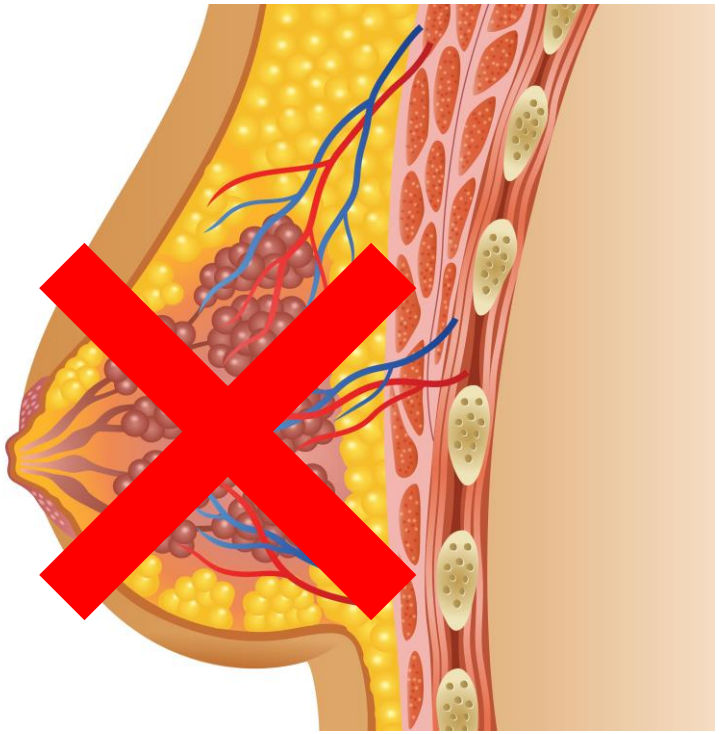
# Immediate breast reconstruction with expander



# Permanent side effects

- Inability to breastfeed
- No or poor skin sensibility
- Different feeling
- Potential chronic pain in the chest area



# Risk of surgical complications

- Infection→ potential explantation
- Wound healing problems
- Hematoma
- Seroma
- Skin necrosis
- Ugly scars
- Capsular contracture
- Implant leakage
- Breast implant-associated large cell anaplastic lymphoma

# DBCG guidelines from 2024

## Bilateral risiko-reducerende mastektomi hos kvinder uden tidligere brystkræft.

1. Kvinder som tilhører risikokategorien "væsentligt øget risiko for brystkræft"* skal tilbydes samtale om fordele og ulemper ved bilateral risikoreducerende mastektomi (BRRM), og skal - under hensyntagen til alder og comorbiditet - tilbydes operation, hvis det ønskes (A). Bærere af disponerende variant med høj penetrans i BRCA1 informeres om, at et nyere studie tyder på, at overlevelsen forbedres ved BRRM (A)

# Effects on breast cancer rates and mortality

# Bilateral risk-reducing mastectomy

## Breast cancer rates

## Overall survival

↓ 90–95%

↑ BRCA1

Breast cancer after bilateral risk-reducing mastectomy

Skytte A-B, Crüger D, Gerster M, Lænkholm A-V, Lang C, Brøndum-Nielsen K, Andersen MK, Sunde L, Kølvraa S, Gerdes A-M.
Breast cancer after bilateral risk-reducing mastectomy.
Clin Genet 2011: 79: 431–437. © John Wiley & Sons A/S, 2011

This study aims to evaluate the incidence of breast cancer after

A-B Skytte[a,b], D Crüger[a], M Gerster[c], A-V Lænkholm[d], C Lang[e], K Brøndum-Nielsen[f,g], MK Andersen[h], L Sunde[i], S Kølvraa[a,b] and A-M Gerdes[g,h,j]

0.8% /PY and HR 0.455 (p=0.224)

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

Bernadette A. M. Heemskerk-Gerritsen[1] · Agnes Jager[1] · Linetta B. Koppert[2] · A. Inge-Marie Obdeijn[3] · Margriet Collée[4] · Hanne E. J. Meijers-Heijboer[5] · Denise J. Jenner[6] · Hester S. A. Oldenburg[7] · Klaartje van Engelen[8] · Jakob de Vries[9] · Christi J. van Asperen[10] · Peter Devilee[11] · Marinus J. Blok[12] · C. Marleen Kets[13] · Margreet G. E. M. Ausems[14] · Caroline Seynaeve[1] · Matti A. Rookus[6] · Maartje J. Hooning[1]

Received: 27 May 2019 / Accepted: 2 July 2019 / Published online: 13 July 2019


HR 0.40 (95% CI 0.20–0.90)

# Aim

**To estimate the uptake and the oncological effects of RR-BM in women with a pathological variant of the *BRCA1/2* gene and compare breast cancer and death rates to a group of matched controls**

# Eligibility criteria

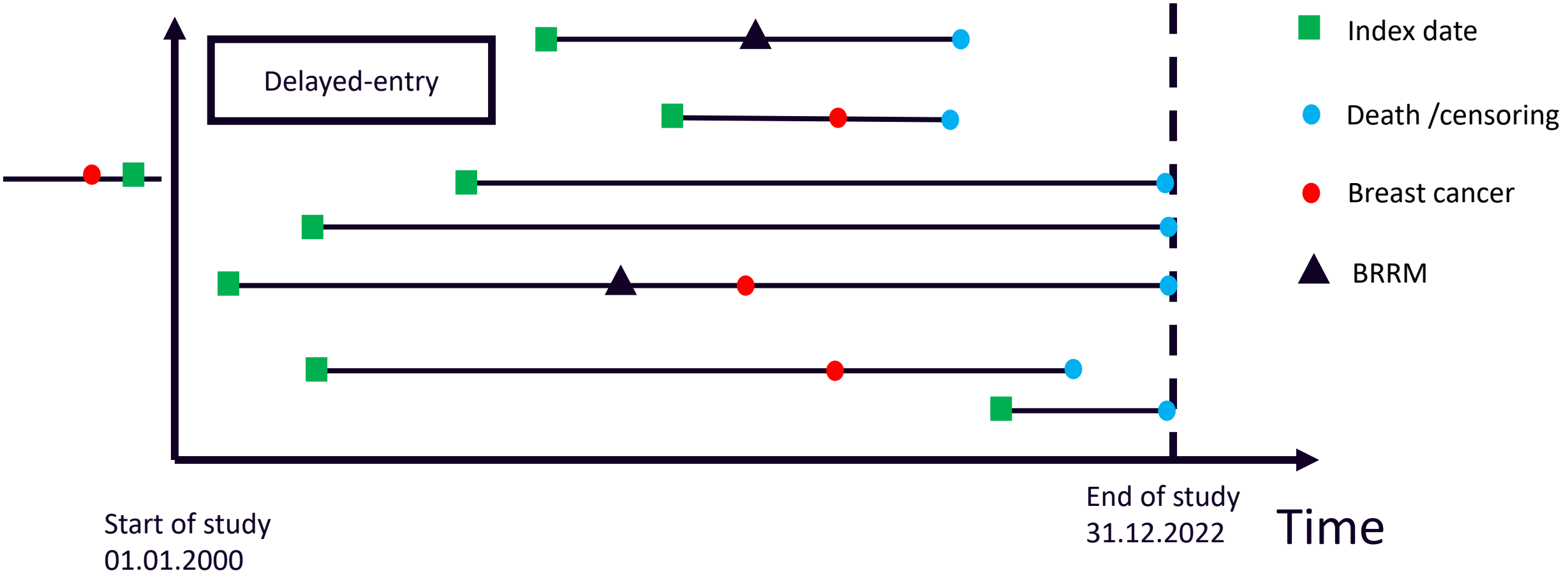
- Women with a class 4 or 5 pathogenic variant in the *BRCA1* or *BRCA2* gene
- No history of cancer (except for non-melanoma skin cancer) at time of genetic test
- Age 18–80 at the time of genetic test
- Alive and resident in Denmark at the time of genetic test

# Data collection from eight national health registers

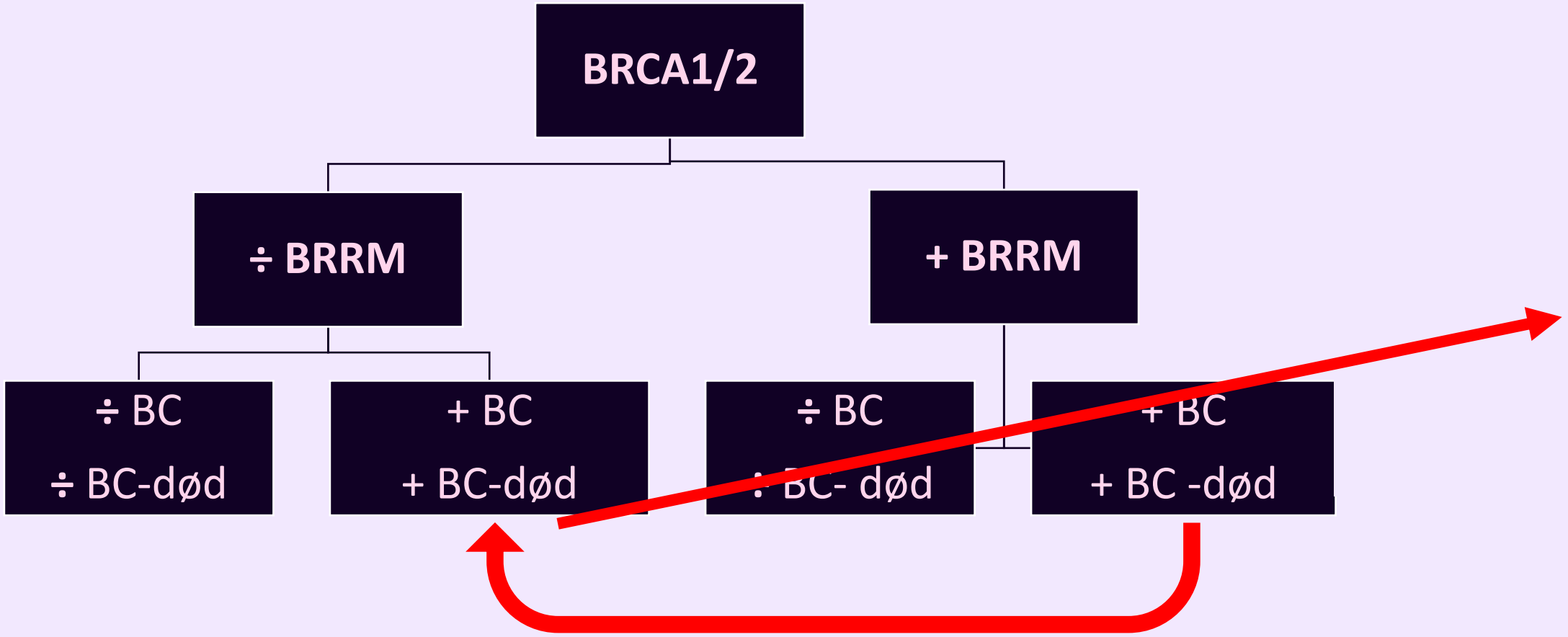
| Register | Data |
| --- | --- |
| **Hereditary Breast and Ovarian Cancer (HBOC) Registry** | BRCA1/2 class 4 or 5 positive women in the period 2000- 2022. |

# Design

## Observations



# Design



# Results

# Results

| Characteristic | BRCA1/2 carriers | Control population | BRCA1 carriers | BRCA2 carriers |
|---|---|---|---|---|

# Number of annually registered unaffected BCRA1/2 carriers increased over time

Rigshospitalet

Til gavn for den enkelte patient og det samlede sundhedsvæsen

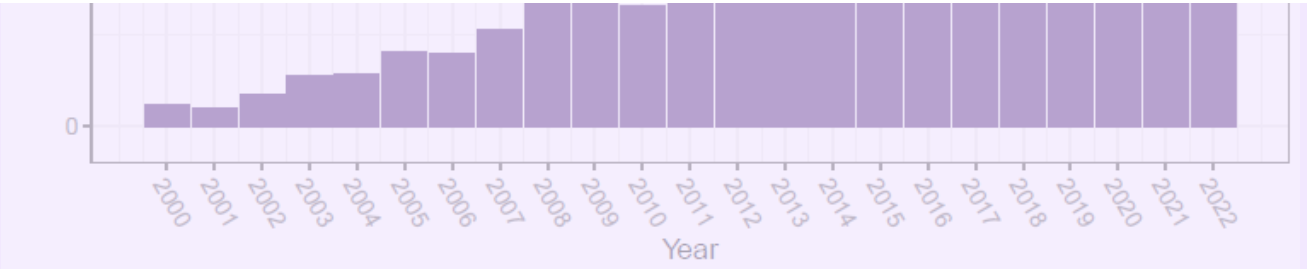
For borgere For fagfolk

SØG MENU

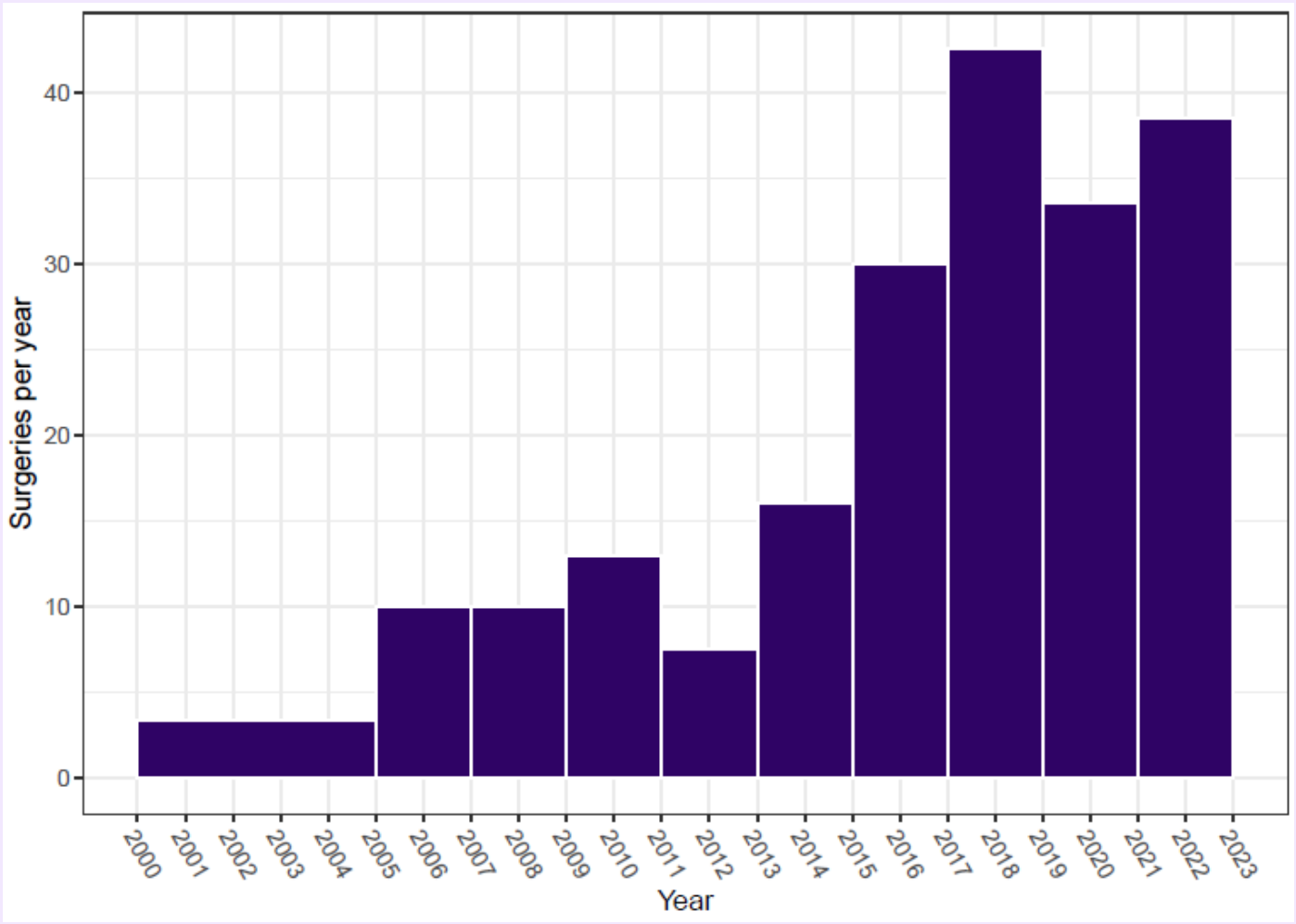
Forside / Forskning / Aktuelle temaer / Gentest bliver standardtilbud ved kræft i underlivet

## Gentest bliver standardtilbud ved kræft i underlivet

For første gang får alle danske patienter med en bestemt sygdom tilbud om en genanalyse. Resultaterne kan bruges i behandlingen og til rådgivning af pårørende.



# Number of annual risk-reducing bilateral mastectomies increased over time



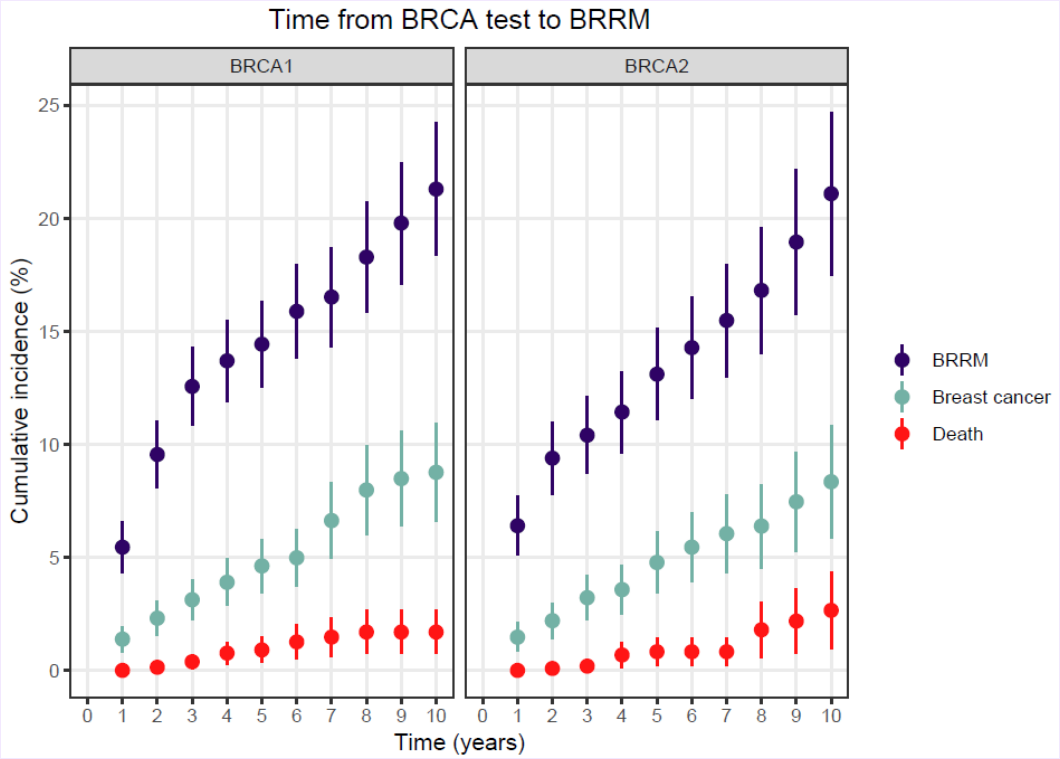
# …and so did the number of breast reconstructions

| Characteristic | BRCA1/2 carriers (N= 3067) | BRCA1 carriers (n= 1649) | BRCA2 carriers (n= 1418) | p-value |
|---|---|---|---|---|
| **Breast reconstruction, N (%)** | | | | |
| - No | 34 (8) | 20 (8) | 14 (8) | |
| - Immediate | **366 (87)** | 208 (87) | 158 (88) | |
| - Secondary | 19 (5) | 12 (4) | 7 (4) | 0.8758 |

www.gettyimages.dk

# Uptake of risk-reducing bilateral mastectomy

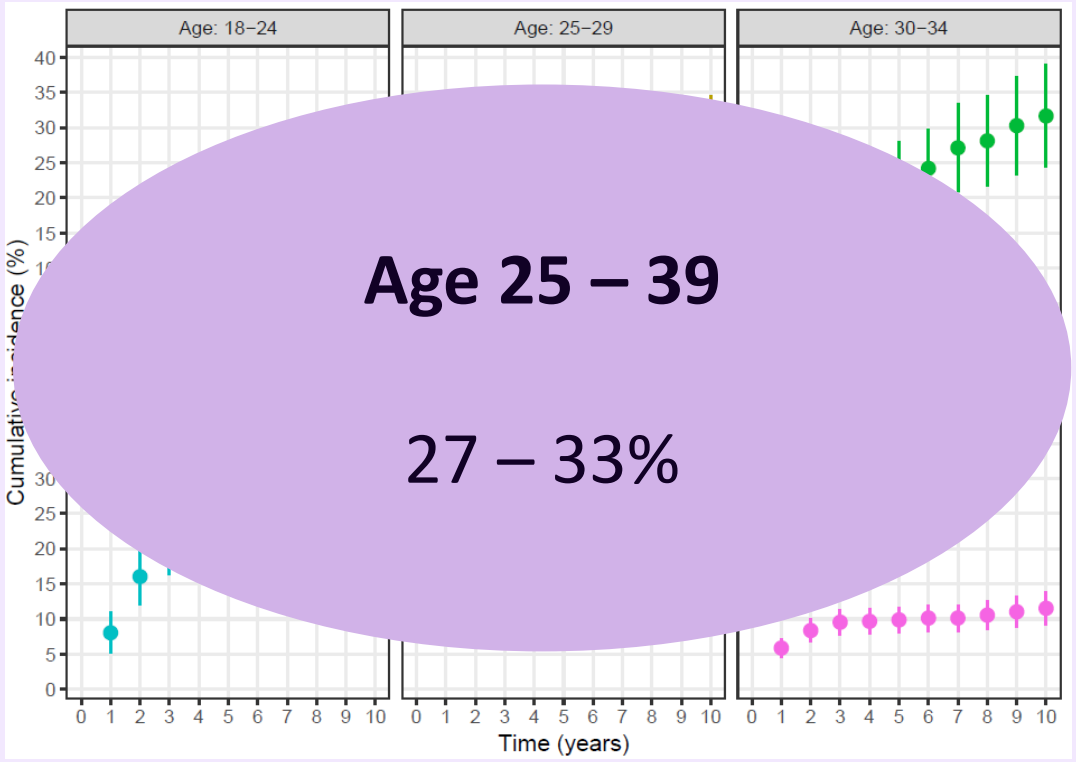
10 years after genetic test disclosure



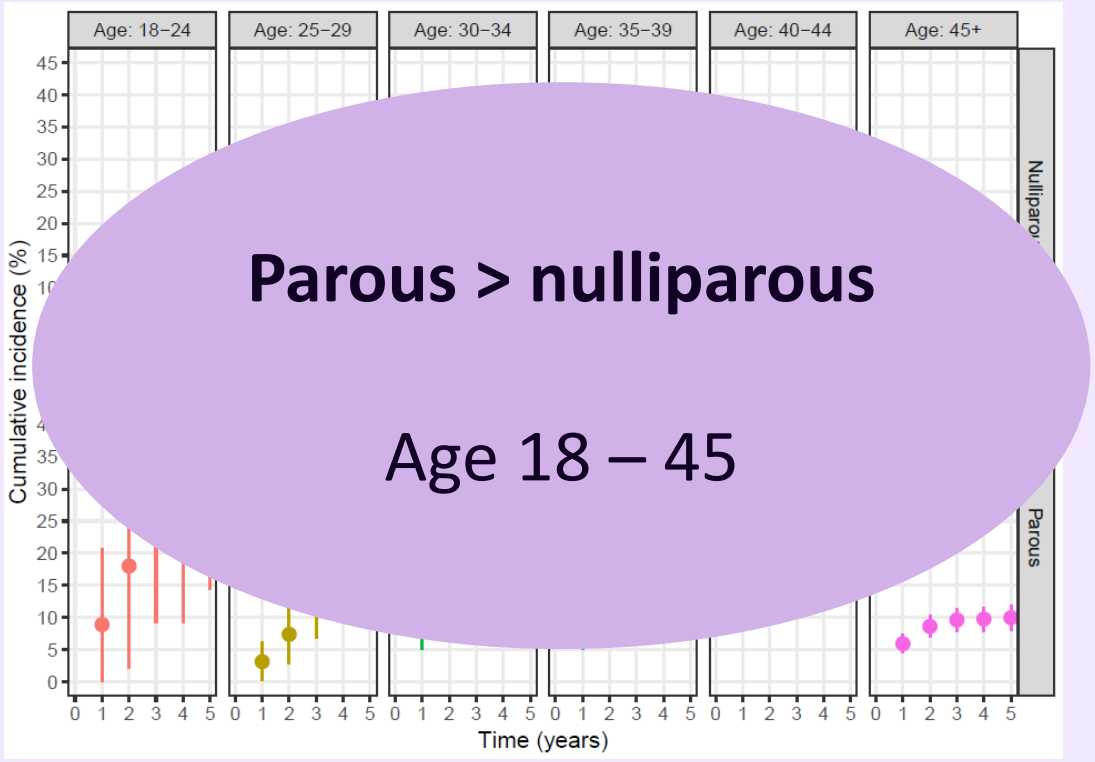

Competing risk models with breast cancer and death as competing risks

# BRRM uptake depend on age and parity

10 years after genetic test disclosure




5 years after genetic test disclosure



# Events and causes of death

| | *BRCA1/2* carriers (N= 3,067) | | |
|---|---|---|---|
| **Event, N** | **BRRM (n= 419)** | **No BRRM (n= 2,648)** | **Matched controls (n= 30,652)** |
| Breast cancer | < 5 | 153 | 281 |
| Death | < 5 | 49–53 | 488 |
| Causes of death | | | |
| - Breast cancer | 0 | 11 | 14 |
| - Ovarian cancer | < 5 | 7 | 7 |
| - Other malignancy | < 5 | 17 | 138 |
| - Non-malignant | 0 | 15 | 300 |
| - Unknown | 0 | < 5 | 29 |

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# Time to event analyses: breast cancer for *BRCA1/2* carriers

| Breast cancer | Person years at risk | Number of events | Unadjusted HR (CI) | p-value | Adjusted HR (CI)* | p-value |
|---|---|---|---|---|---|---|
| **BRCA1/2 carriers** | | | | | | |
| **Risk-reducing surgery status** | | | | | | |
| - **No risk-reducing surgery** | 10,952 | 105 | 1.00 | | 1.00 | |
| - **BRRM** | 2,834 | < 5 | 0.06 (0.01–0.24) | < 0.0001 | 0.06 (0.01—0.25) | < 0.0001 |

Cox proportional hazard models. Stratified to allow for different baseline hazards for each BRCA gene subtype

*Adjusted for parity and age at first childbirth

# Time to event analyses: breast cancer for *BRCA1/2* carriers and controls

| Breast cancer | Person years at risk | Number of events | Unadjusted HR (CI) | p-value | Adjusted HR (CI)* | p-value |
|---|---|---|---|---|---|---|
| **BRCA1/2 carriers and the matched control population** | | | | | | |
| - **Matched control** | 174,997 | 281 | 1.00 | | 1.00 | |
| - **BRCA 1/2 carrier without BRRM** | 14,128 | 153 | 6.81 (5.59–8.29) | < 0.0001 | 7.40 (5.81–9.42) | < 0.0001 |
| - **BRCA 1/2 carrier after BRRM** | 2,834 | < 5 | 0.43 (0.11–1.75) | 0.240 | 0.47 (0.12–1.90) | 0.287 |

Cox proportional hazard models. Stratified to allow for different baseline hazards for each BRCA gene subtype

*Adjusted for parity and age at first childbirth

# Time to event analyses: overall mortality for *BRCA1/2* carriers

| Overall mortality | Person years at risk | Number of events | Unadjusted HR (CI) | p-value | Adjusted HR (CI)* | p-value |
|---|---|---|---|---|---|---|
| **BRCA1/2 carriers** | | | | | | |
| **Risk-reducing surgery status** | | | | | | |
| - **No risk-reducing surgery** | 11,262 | 36 | 1.00 | | 1.00 | |
| - **BRRM** | 2,844 | < 5 | 0.35 (0.10–1.16) | 0.087 | 0.34 (0.10–1.15) | 0.083 |

Cox proportional hazard models. Stratified to allow for different baseline hazards for each BRCA gene subtype

*Adjusted for parity and age at first childbirth

# Time to event analyses: overall mortality for *BRCA1/2* carriers and controls

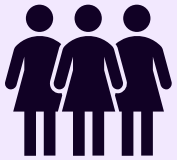
| Overall mortality | Person years at risk | Number of events | Unadjusted HR (CI) | p-value | Adjusted HR (CI)* | p-value |
|---|---|---|---|---|---|---|
| **BRCA1/2 carriers and the matched control population** | | | | | | |
| **BRRM status** | | | | | | |
| - **Matched control** | 176,311 | 488 | 1.00 | | 1.00 | |
| - **BRCA 1/2 carrier without BRRM** | 15,034 | 50 | 1.13 (0.84–1.51) | 0.415 | 1.41 (0.99–2.02) | 0.057 |
| - **BRCA 1/2 carrier after BRRM** | 2,844 | < 5 | 0.66 (0.21–2.07) | 0.479 | 0.81 (0.26–2.59) | 0.730 |

Cox proportional hazard models. Stratified to allow for different baseline hazards for each BRCA gene subtype

*Adjusted for parity and age at first childbirth

# Strengths and limitations

## Strengths



Large number of patients

National health registers

## Limitations

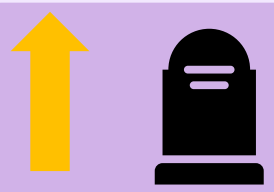
Not representative of all Danish *BRCA1/2* carriers

Short follow-up time

# Conclusions

RR-BM reduces breast cancer incidence significantly

RR-BM seemed to reduce mortality, but not significantly



No RR-BM seemed to increase mortality compared to the background population, but not significantly

# In five to ten years

**REPEAT**

# Psychological aspects of a risk-reducing mastectomy and immediate breast reconstruction

# Background

## BRCA1/2 pathogenic variant

72 and 69 % risk

42 and 49 years

Quality of life, anxiety, depression, worry

## Bilateral risk-reducing mastectomy

2–5% risk

BRCA1 better overall survival

Permanent side effects

60% choose surgery at age 50 in Denmark

Alignment of expectations

# The problem with previous studies

- Questionnaires not specific or validated
- Outdated studies
- No baseline measurement
- No prospective comparison with surveillance

# The HEBRECA study

## Quality of life and hereditary risk of developing breast cancer

# The HEBRECA study

## Quality of life and hereditary risk of developing breast cancer

HEBRECA

Data collection Apr 2019 to Jul 2023

Departments of plastic surgery, radiology, and clinical genetics

Cancer-free women with high risk of developing breast cancer

# Validated patient-reported outcome measurement instruments

- BREAST-Q
- Patient Health Questionnaire-9 (PHQ-9)
- General Anxiety Disorder-7 (GAD-7)
- Concerns About Recurrence Questionnaire-3 (CARQ-3)
- Sociodemographic information
- Parity, family history, chronic health conditions, menopause, bilateral-salpingo-oophorectomy

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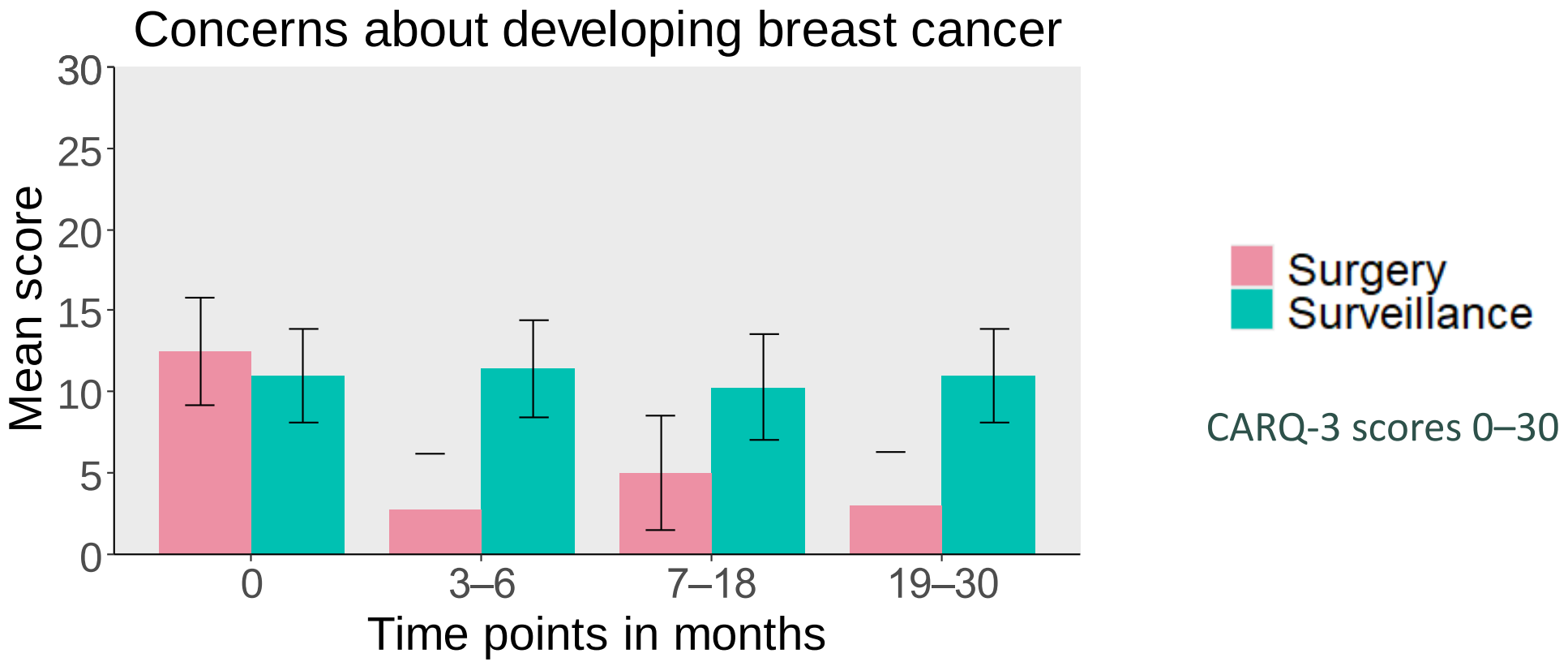
# Mean number of responses, counts (%)

| | Baseline | 3–6 months | 7–18 months | 19–30 months |
|---|---|---|---|---|
| Surgery | 33 (94) | 22 (64) | 23 (65) | 19 (53) |
| Surveillance | 36 (98) | 29 (73) | 25 (68) | 27 (74) |

# Outcomes from linear mixed model for repeated measurements

- Surveillance group differences
- Between-gruop differences
- Differences in development over time (interaction)

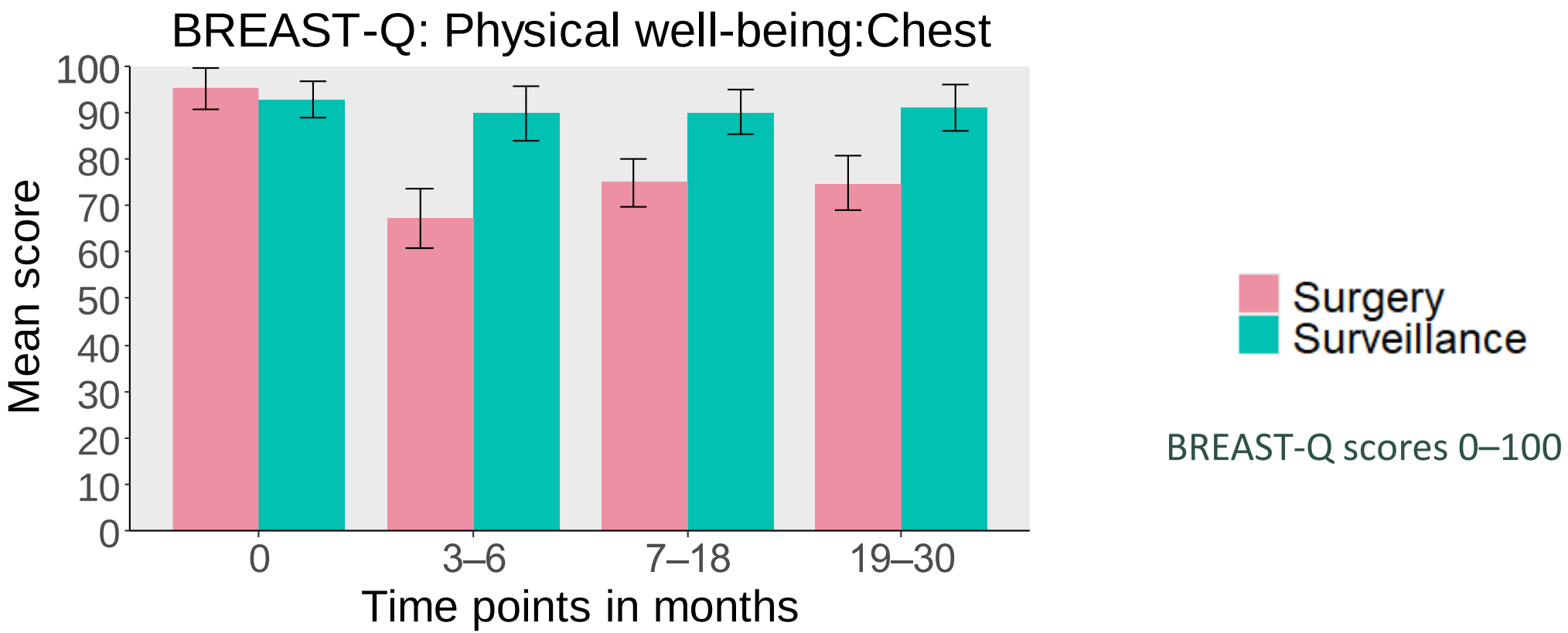
# Concerns about developing breast cancer decreases




CARQ-3 scores 0–30

Analyses were conducted using a linear mixed model for repeated measurements and adjusted for age, parity, first-degree relatives with breast cancer, and level of education.

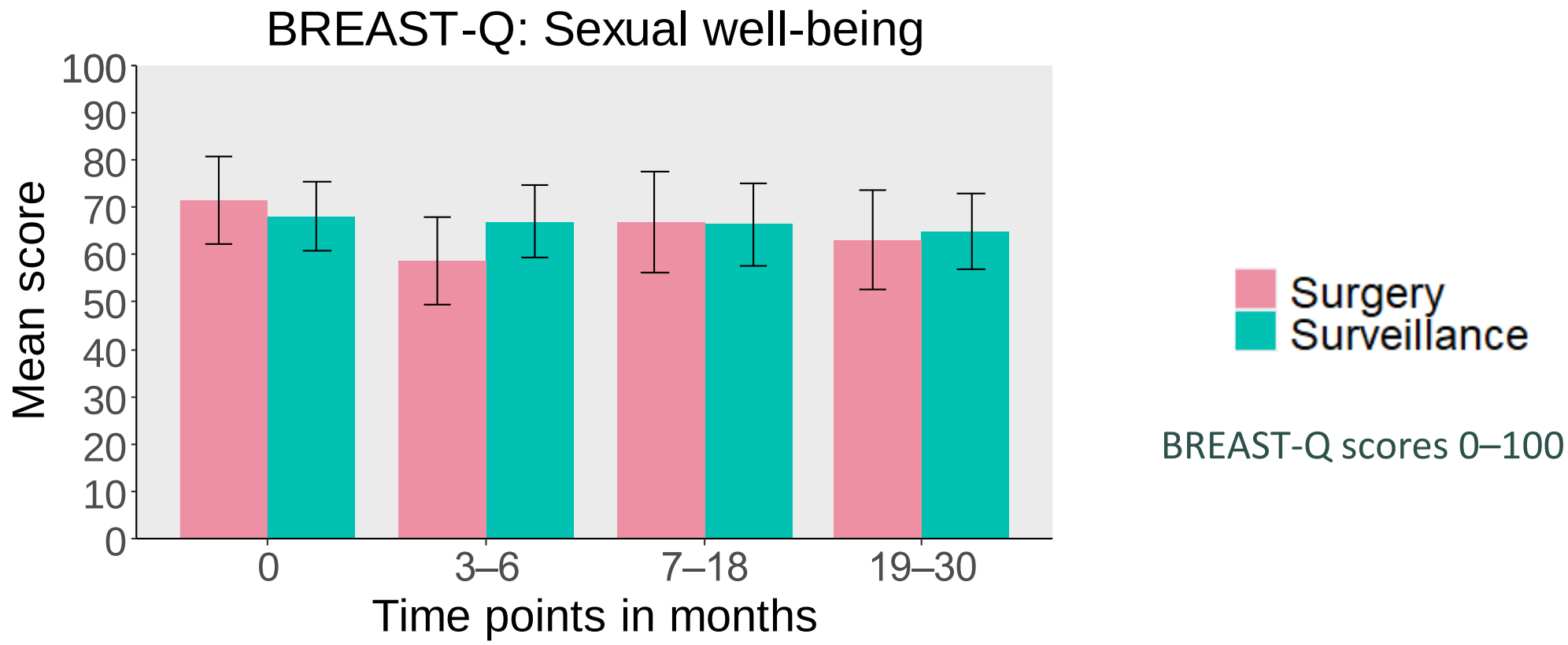
# Physical well-being of the chest decreases




BREAST-Q scores 0–100

Analyses were conducted using a linear mixed model for repeated measurements and adjusted for age, parity, first-degree relatives with breast cancer, and level of education.

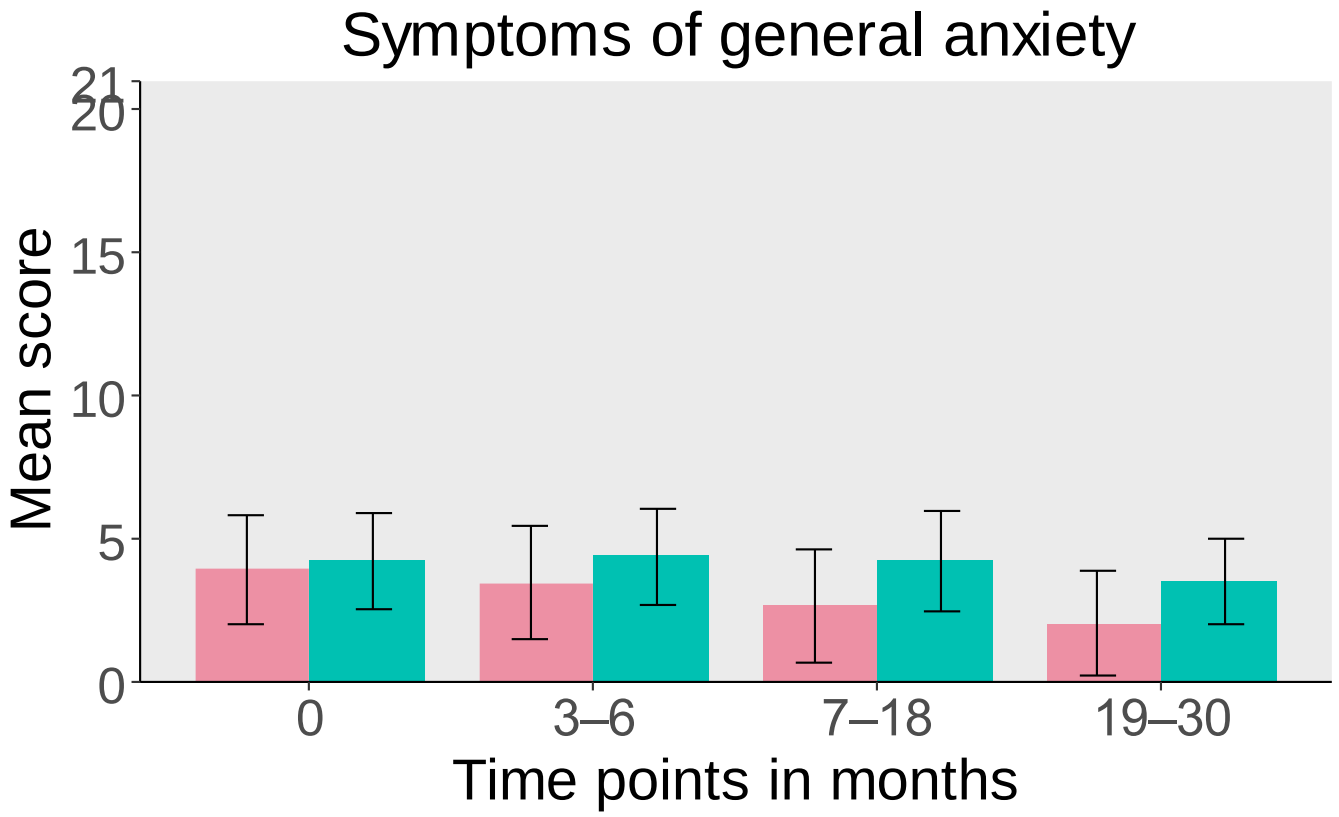
# Sexual well-being decreases in short term




BREAST-Q scores 0–100

Analyses were conducted using a linear mixed model for repeated measurements and adjusted for age, parity, first-degree relatives with breast cancer, and level of education.

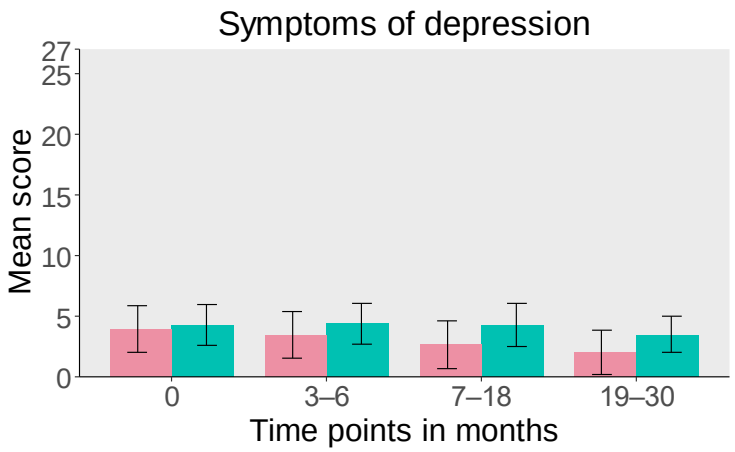
# General anxiety decreases in long term

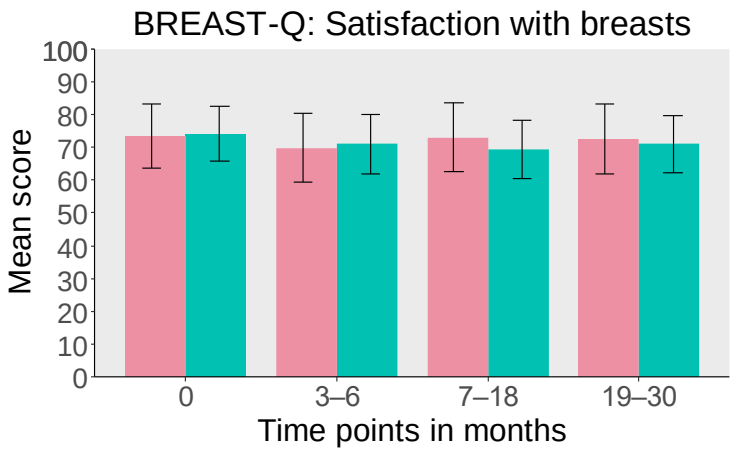


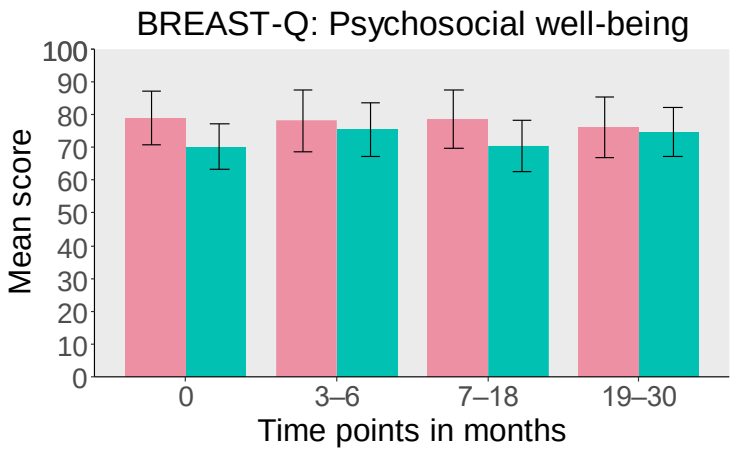

GAD-7 scores 0–21

Analyses were conducted using a linear mixed model for repeated measurements and adjusted for age, parity, first-degree relatives with breast cancer, and level of education.

# No differences in symptoms of depression, satisfaction with breasts or psychosocial well-being

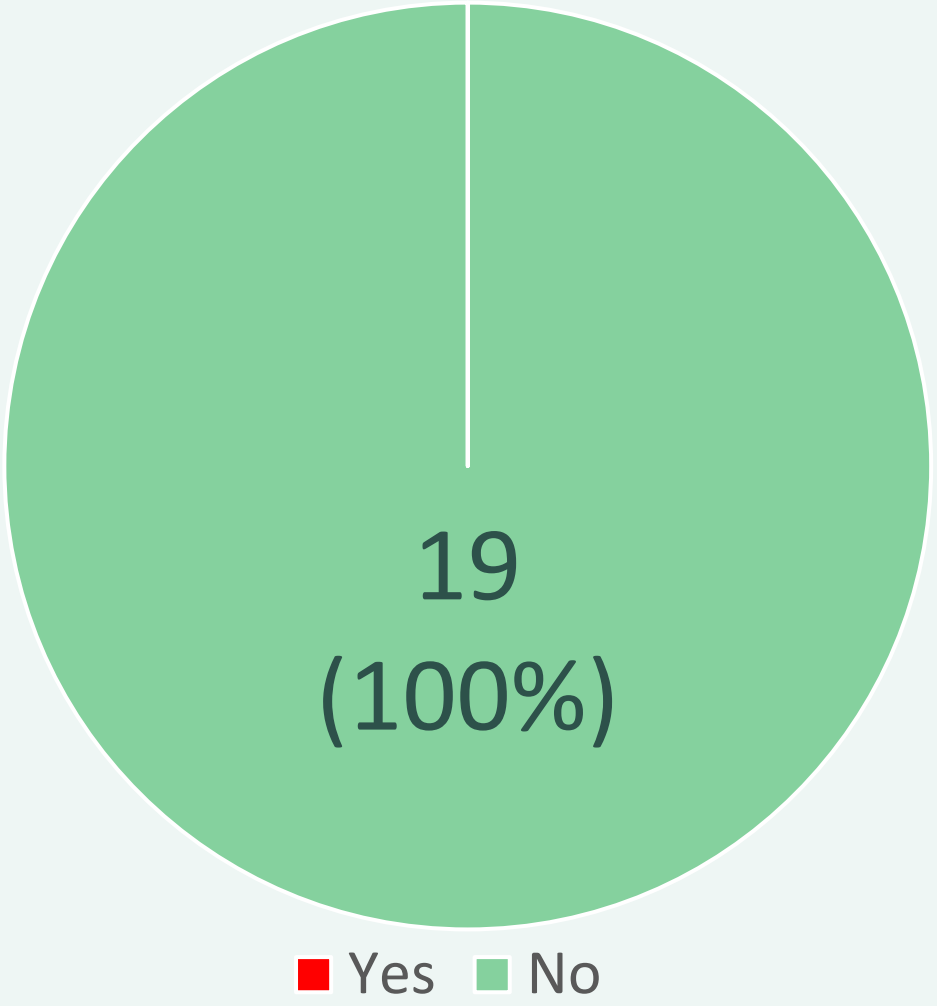



Surgery
Surveillance

# No patients regretted 7–18 months postoperatively



# Strenghts and limitations

## Limitations

- Small number of patients
- Selection/volunteer bias
- Non-randomized

## Strenghts

- Baseline assessment
- Mostly validated and specific questionnaires
- Prospective comparison to surveillance group

# Conclusion

## Surgery versus surveillance

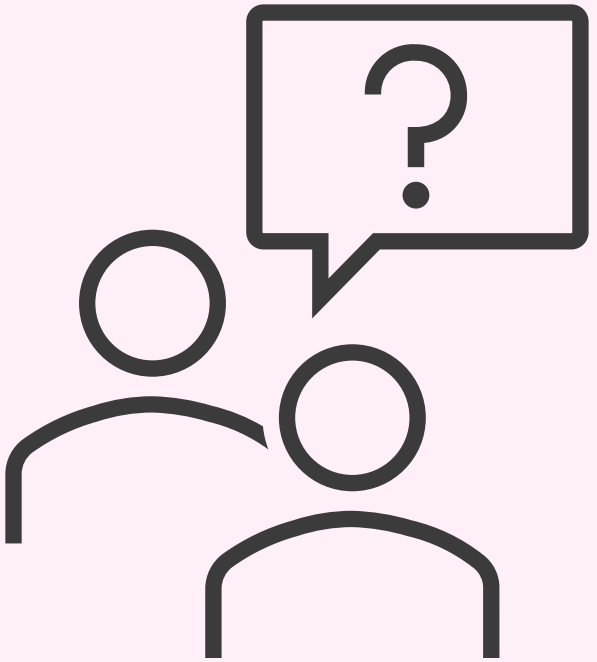
Concerns

Physical well-being: Chest

Both short- and long-term

# Questions?

Thank you to all of the participating departments



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Lisbet Rosenkrantz Hölmich, Pernille Envold Bidstrup, Lene Mellemkjær, Anne-Marie Axø Gerdes and Niels Kroman

cecilie.balslev.willert@regionh.dk