Karolinska Institutet

Karolinska Mammography Project for Risk Prediction of Breast Cancer :

Karma

Risk assessment and prevention of breast cancer

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Outline

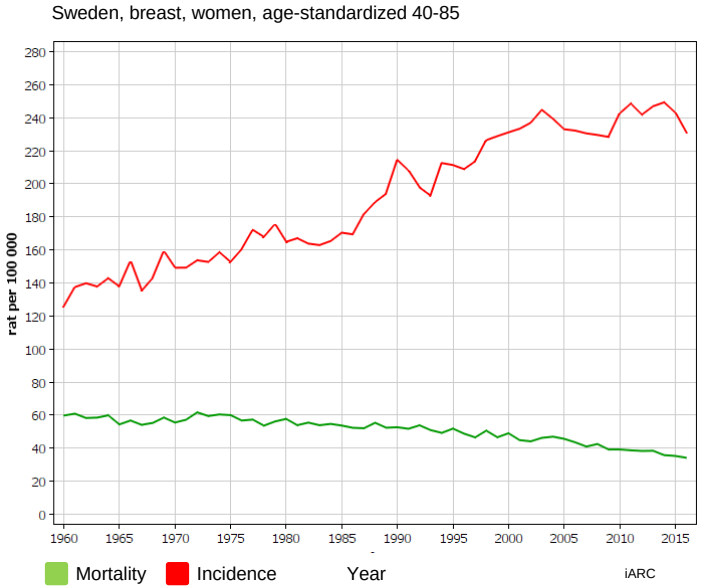
A. Improving mammography screening

B. Prevention of breast cancer

Breast cancer incidence and mortality

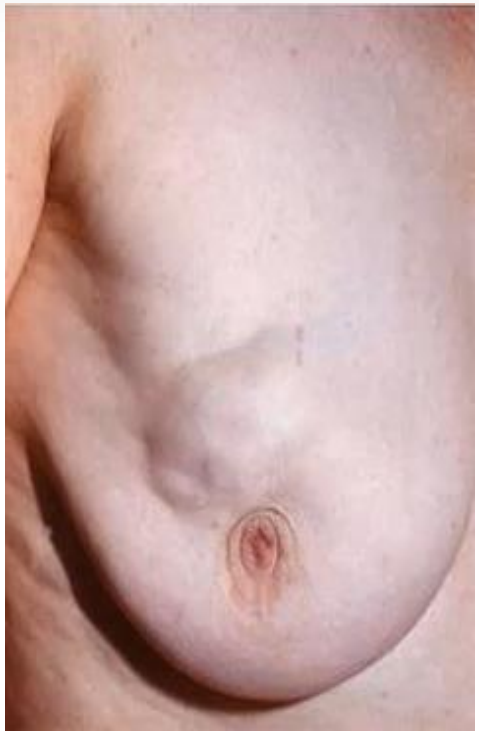
- Approximately 13% of the women in the Western world develop breast cancer during their lifetime
- Yearly, 600,000 women are diagnosed and 150,000 die from breast cancer in the Western world
- Breast cancer incidence is increasing, but mortality is decreasing over the last decades

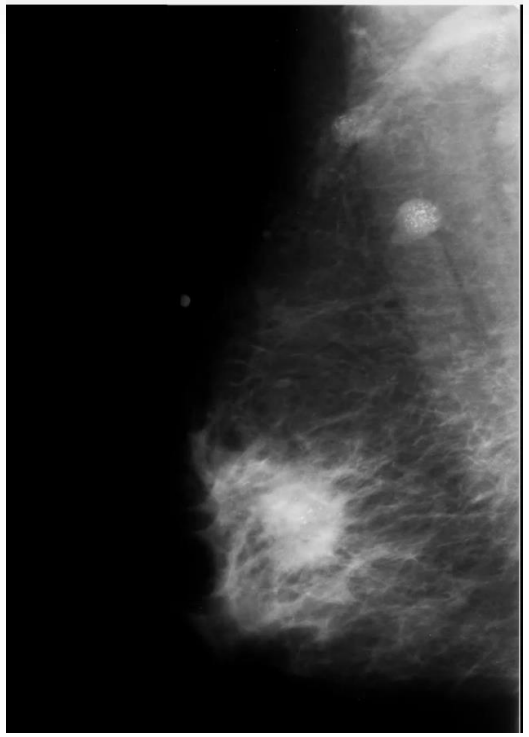
- It is not well understood why the incidence is increasing, but the mortality decreasing is due to early detection and treatment of the tumor.
- Lifestyle factors may be responsible for 30% of the breast cancers



Mammography screening – a life saviour

- Studies show a reduction of breast cancer mortality by 20-40% among women attending mammography screening
- In the ‘70s low-dose mammography was invented and fibro-glandular tissue, microcalcifications, and small cancers could be observed on film





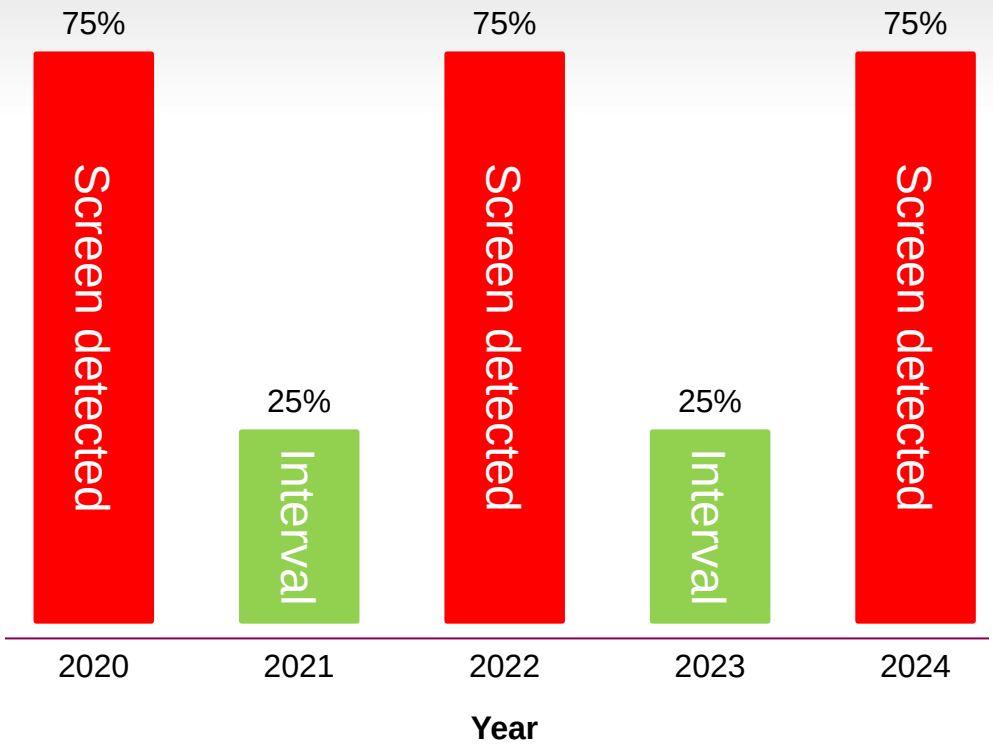
Can mammography screening be further improved?

- A large proportion of women attending mammography screening are sent at home with a negative mammogram, but come back with a cancer before or at next screen
  - 25% of the breast cancers are identified in the interval between screens
  - Interval cancers have 2 times higher 5-year mortality than screen detected cancers
  - A proportion of women present with large tumors at next screen

Idea:

In addition to the detection work-up at current screen exam, make an assessment of the probability that a woman will come back before or at next mammography screen in 2 years.

Proportion of screen detected cancers and interval cancers over time



True interval cancers ~50% of the interval cancers

Hmmm… Is this risk or is it detection?

The idea

In addition to the detection work-up at current screen exam, make an assessment of the probability that a woman will come back before or at next mammography screen in 2 years.

- Tumor progression time is 10 years or more
- Sojourn time (from theoretically detectable to actual diagnosis) is approximately 3 years
- Detection requires that a lesion can be identified and a tumor diagnosed
- Risk tells that there will be a diagnosis within a certain time
  - Maybe it can be detected in 1 year time after an additional examination
  - Maybe it will be detected at next regular screen

Short-term risk of breast cancer

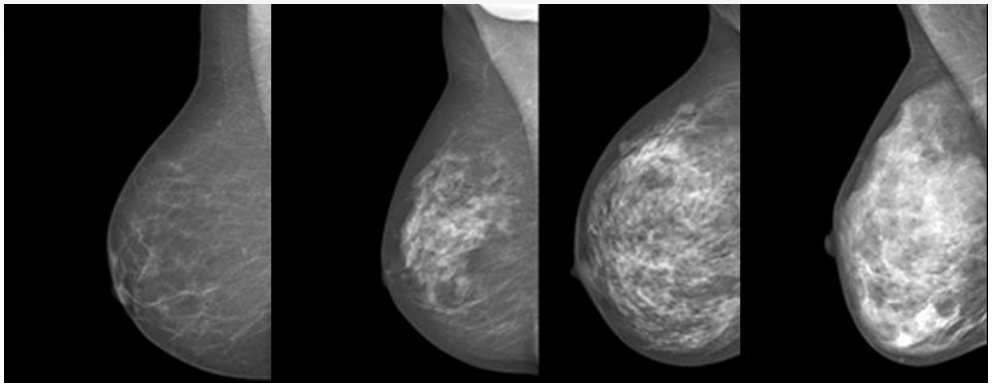
- The short-term risk of a woman means that she has a breast at risk of a future breast cancer diagnosis, but the lesion is unknown
- Short-term risk has a prediction horizon within a 5-year window
- Intervention: screen high-risk women more frequent or with a more sensitive modality
- Short-term risk is assessed at every screening visit

Setting up a risk model for use in mammography screening

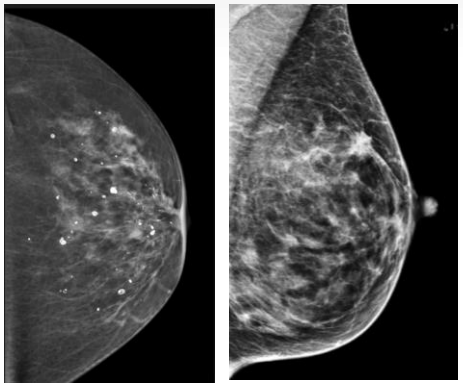
- Risk assessment usually involves family history of breast cancer, lifestyle factors, genetic factors
- Could mammograms be used?
  - Available infrastructure for the general female population
  - Mammographic features are intuitive to radiologists
  - Many traditional risk factors are reflected in mammograms (parity, age at first birth, use of hormone replacement therapy, benign breast disease, prior biopsy)
- A mix of existing and fast-growing cancers is targeted in the women who are sent at home with a negative mammogram and come back with a cancer within 2 years

Factors used in the short-term risk model

Mammographic density, left-right breast asymmetry, age

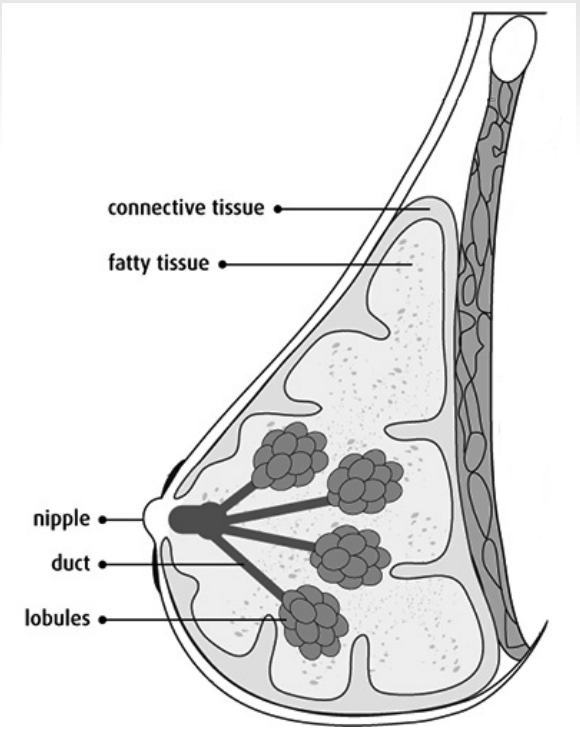


Calcifications / masses, left-right breast asymmetry



OPTIONAL: BMI, menopausal status, family history of breast cancer, hormone replacement therapy, alcohol, tobacco, polygenic risk score (313 SNPs)

The short-term risk model is based on breast anatomy and origin of cancers



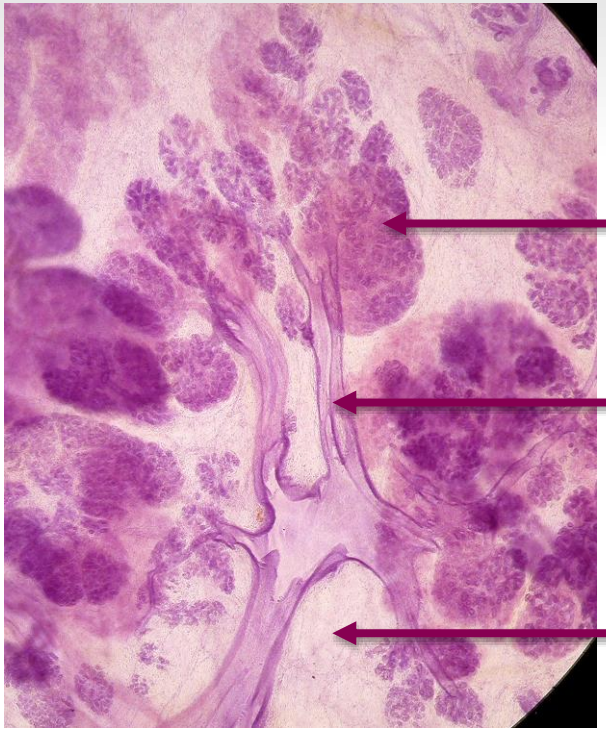
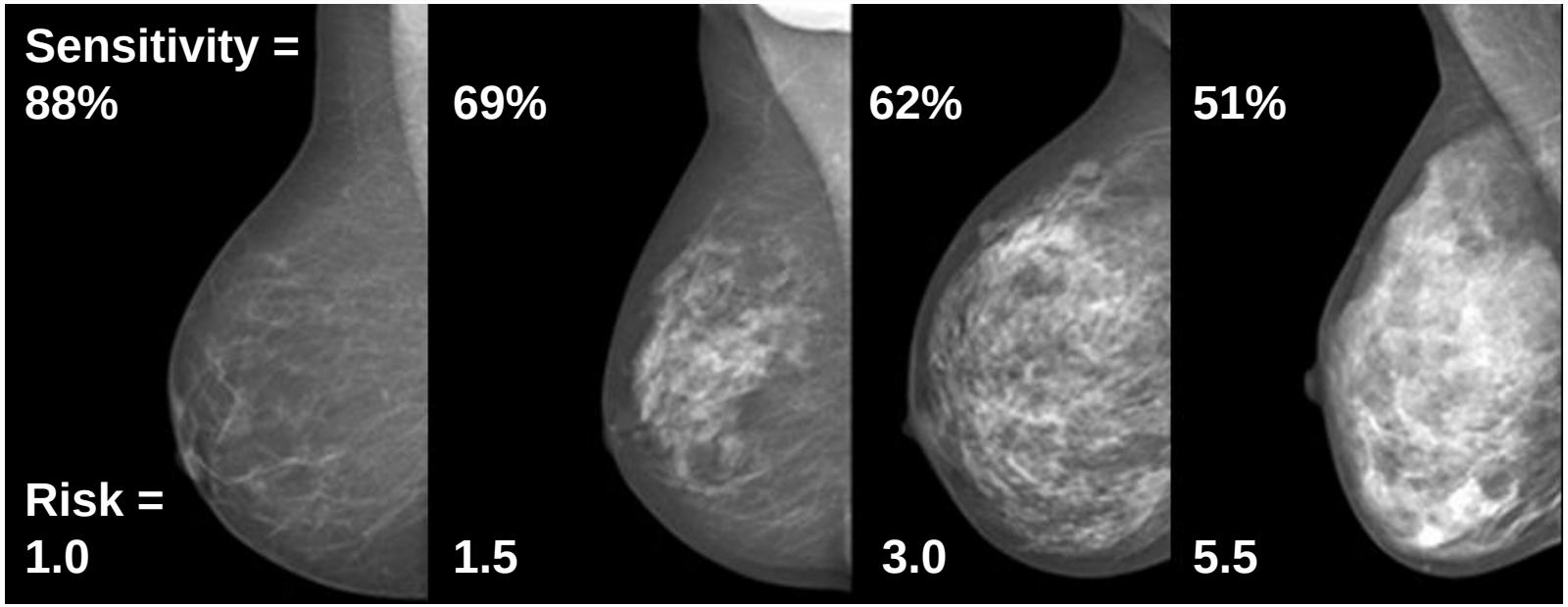


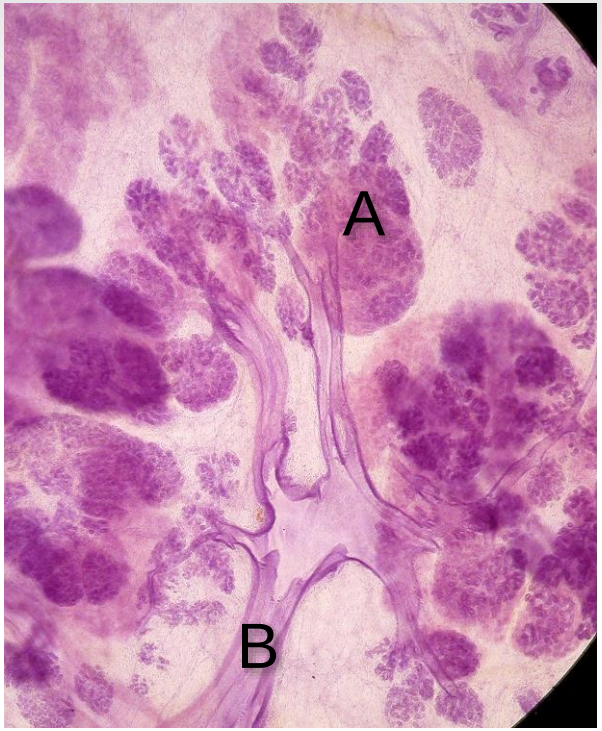
Image: Laszlo Tabar

Mammographic representation of fibro-glandular tissue is included in the risk model

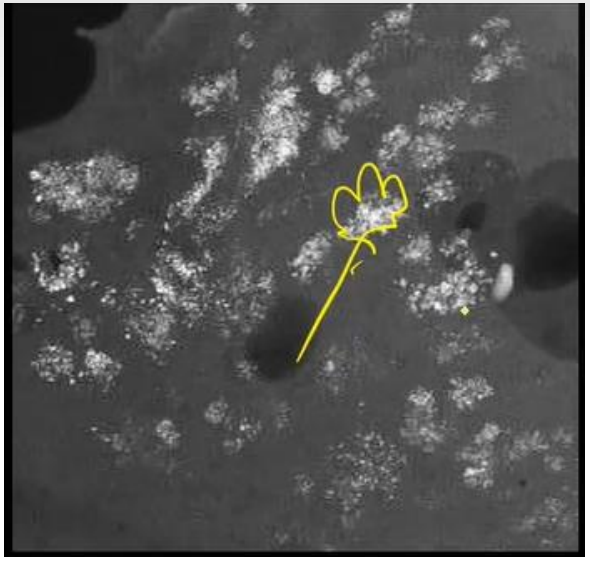
BI-RADS breast composition score



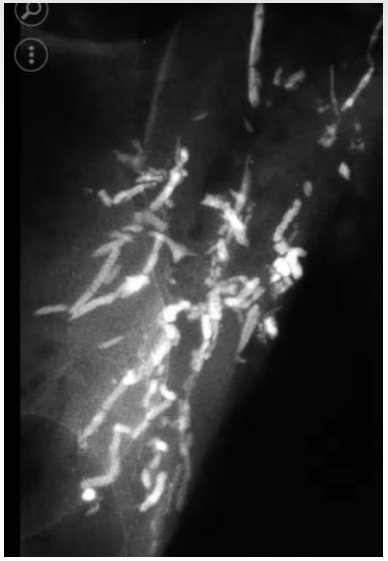
Mammographic representation of microcalcifications is included in the risk model



Images: Laszlo Tabar



A. Clusters in TDLUs

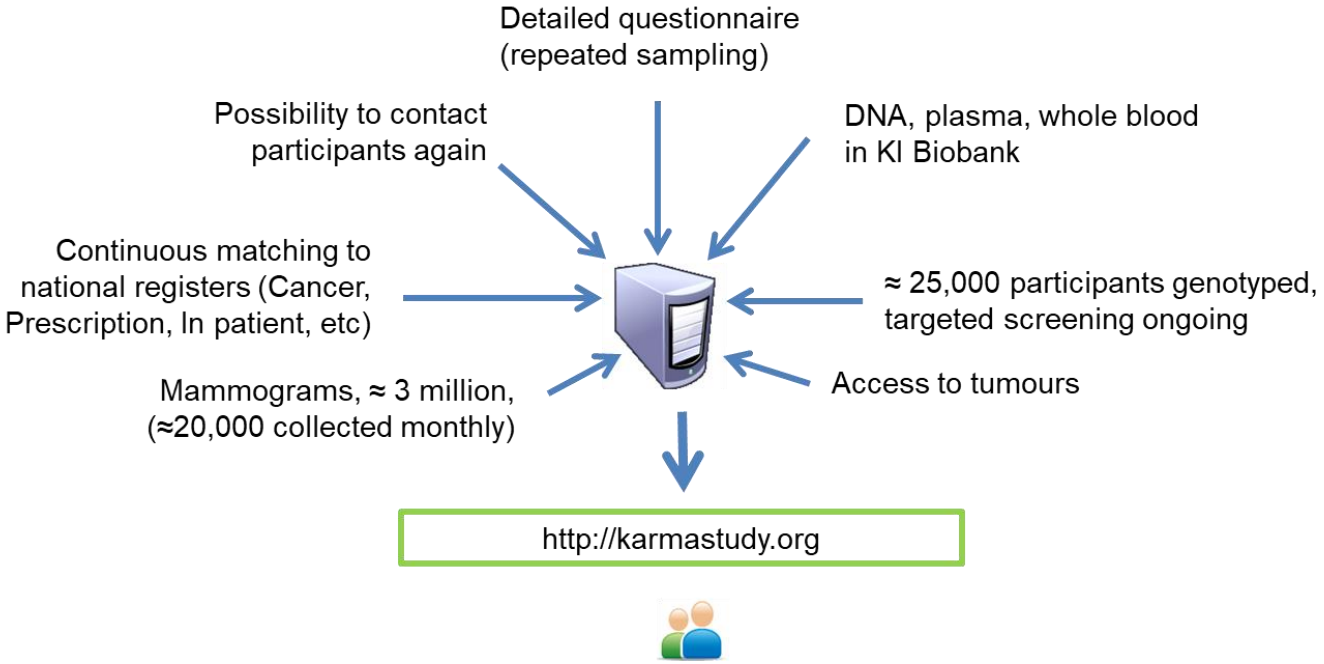


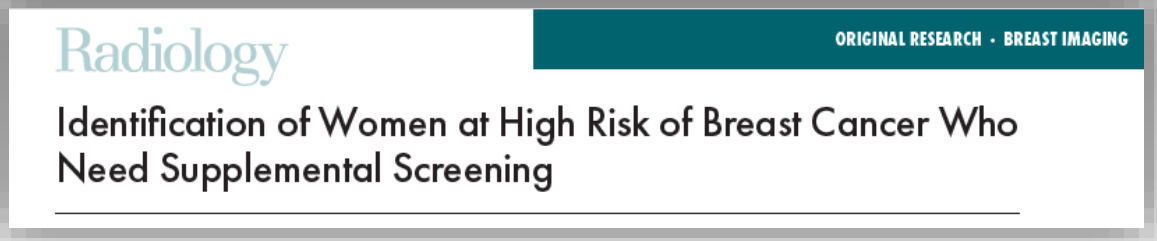
B. Casting type, branching in ducts

Prevalence: 30-50% of invasive cancers
Mechanisms involved: necrosis, epithelial-to-mesenchymal transition

Constructing a risk model starts by collecting lots of data

- KARMA cohort: women recruited between 2011-2013 from four hospitals in Sweden
- 70,877 women included, 34% of screened women





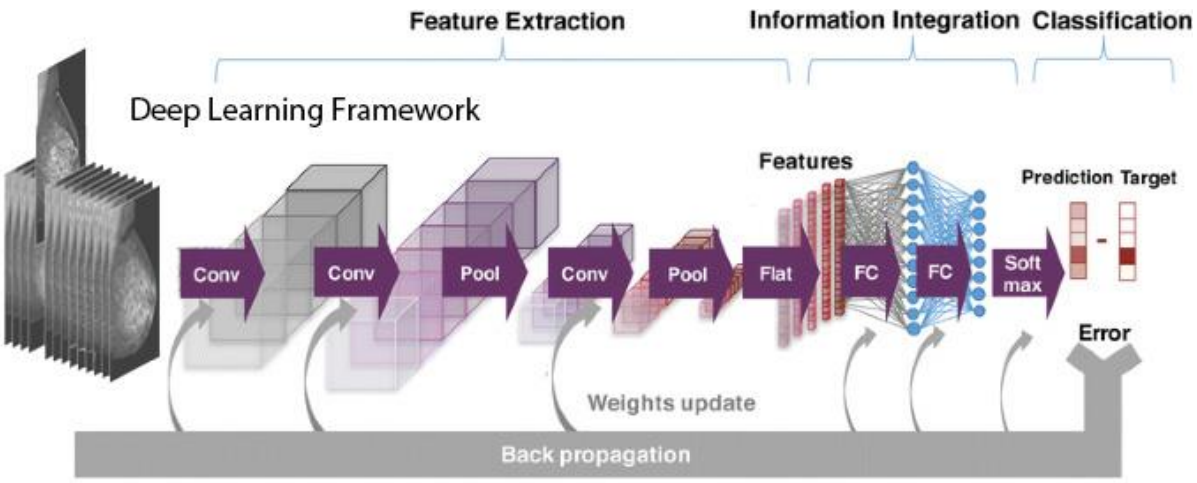
Study population

- The study was based on a case-cohort sample of the KARMA cohort including 974 breast cancer cases and 9,376 healthy women

- External mammography screening validation cohorts:
  - Malmö MBTST (104 cancers, 9,745 healthy women)
  - Karolinska CSAW (613 cancers, 8,489 healthy women)
  - KARMA external validation (179 cancers, 9,491 healthy women)

Risk model construct

- Deep convolutional neural network based on an input of images (left hand side) and results in a prediction of breast cancer status (right hand side).



Three models were constructed

- Model 1: An image-based risk model was developed using STRATUS and iCAD mammographic features (density, microcalcifications, masses), left-right breast differences of features, and age

- Model 2: The lifestyle extended model also included menopause status, family history of breast cancer, body-mass-index, hormone replacement therapy, and use of tobacco and alcohol

- Model 3: The genetic extended model also included a polygenic risk score with 313 single nucleotide polymorphisms

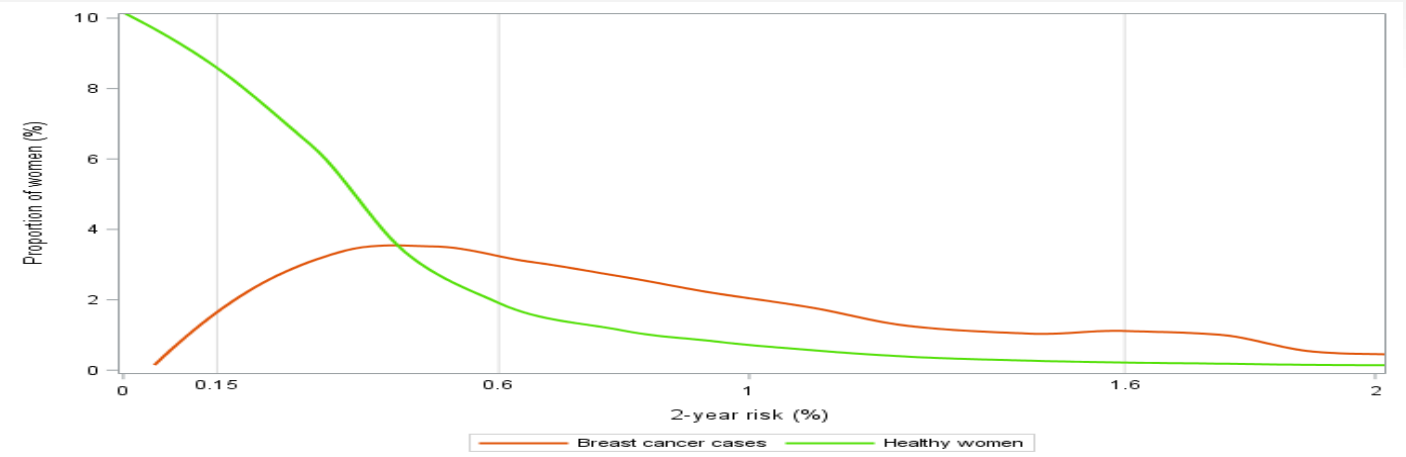
A model is checked for its ability to identify breast cancer cases among all healthy women

Model	AUC (95% CI)
KARMA case-cohort (974 cancers, 9,376 healthy women)	
1. Model 1: mammographic density, microcalcifications, masses, age	0.73 (0.71,0.74)
2. Model 2: Model 1 + lifestyle and familial risk factors	0.74 (0.72,0.75)
3. Model 3: Model 2 + PRS	0.77 (0.75,0.79)
MBTST cohort (104 cancers, 9,745 healthy women), Model 1	0.71 (0.67,0.75)
CSAW (613 cancers, 8,489 healthy women), Model 1	0.73 (0.71,0.76)
KARMA external validation set (179 cancers, 9,491 healthy women), Model 1	0.73 (0.69, 0.77)
Polygenic risk score (313 SNPs) + mammographic density	0.67 (0.65,0.69)
Tyrer-Cuzick + mammographic density	0.62 (0.60,0.64)
Gail + mammographic density	0.61 (0.60,0.63)

A model published by Yala et al. at MIT last year had AUC: 0.71

A risk model is checked for its ability to identify groups of women what should have an intervention, e.g. supplemental screening

Risk category classification based on clinical guideline for recommended follow-up of women at increased risk of breast cancer. The 10-year risk categorization was adapted to 2-year risk.



Risk groups	Percent women at risk	Absolute 2-year risk (%)	Relative risk
0-0.15 (low)	26.7	0.09	0.3
0.15-<0.6 (general)	48.2	0.29	1.0 (reference)
0.6-<1.6 (moderate)	17.3	0.87	3.0
≥1.6 (high)	7.8	2.70	9.4

So, can mammography screening improve further?

- Approximately 25% of the cancers present in the interval between mammography screens with ~2 times increased 5-year breast cancer mortality

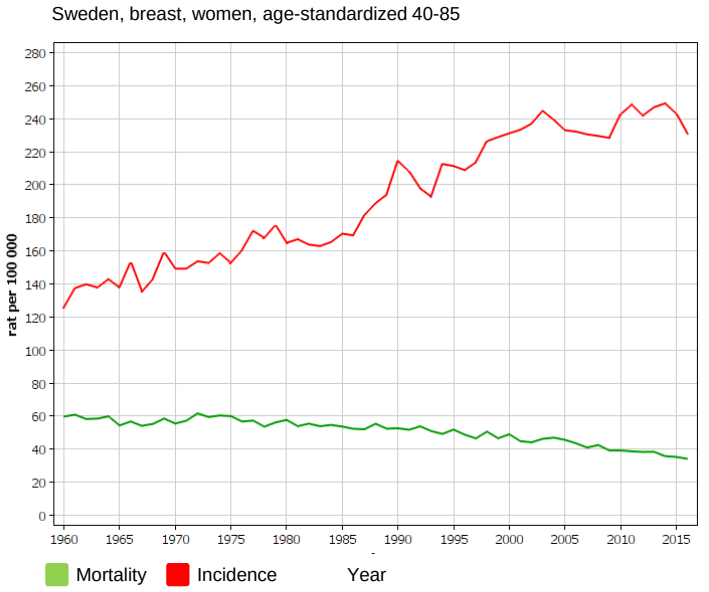
- A risk model can be constructed that complements current detection work-up and identifies the short-term risk with an AUC >0.70

- A prospective study is needed to test the risk model in clinical praxis, where women are invited based on risk of cancer and compared with standard of care
  - Will a larger proportion of aggressive cancers be detected?
  - What is the health economy of risk based screening?

B. Prevention of breast cancer

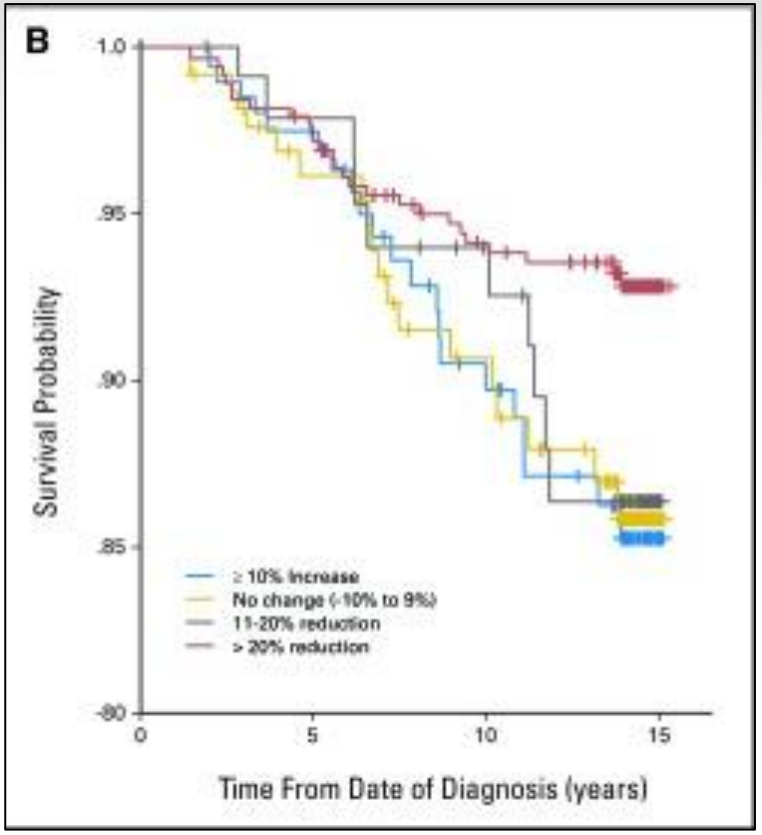
A short background

- Breast cancer incidence increase over time ~1.5% per year
- A healthier lifestyle could reduce breast cancer incidence
  - BMI, physical activity, use of alcohol, smoking
- Medication
  - Tamoxifen reduces breast cancer incidence
  - Menopausal like side-effects
    (hot flashes, cold sweats, sexual, gynaecological)
  - Side-effects must be reduced
  - Not all women benefit from the medication.
    An early marker is needed to identify responders.



Tamoxifen improves long-term survival in breast cancer patients

- Li et al. showed that women who experienced a mammographic density reduction >20% within 2 years of tamoxifen use had ~50% better 15-year survival compared to women who had <20% density reduction.



Tamoxifen reduces breast cancer incidence in high-risk women who decrease in mammographic density

- Cuzick et al. showed that ~50% of the women using tamoxifen for 1.5 years had >10% density reduction and these women had a ~65% decrease in 8-year breast cancer incidence compared to women with no change in density

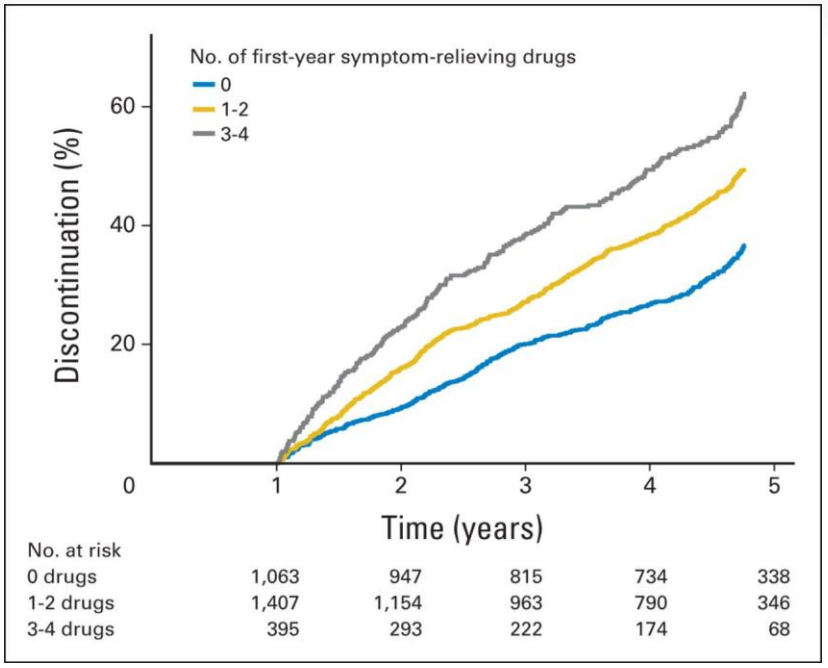
Variable	No. of control subjects/No. of case subjects	Tamoxifen, all	Tamoxifen, breast density reduction <10%		Tamoxifen, breast density reduction ≥10%	
		OR (95% CI)	No. of case subjects	OR (95% CI)	No. of case subjects	OR (95% CI)
Overall	929/120	0.73 (0.49-1.08)	35	1.13 (0.72-1.77)	13	**0.37 (0.20-0.69)**

A large proportion of women discontinue their tamoxifen treatment due to side-effects

- He et al. showed that ~50% of the women discontinued their treatment within 5-years of treatment

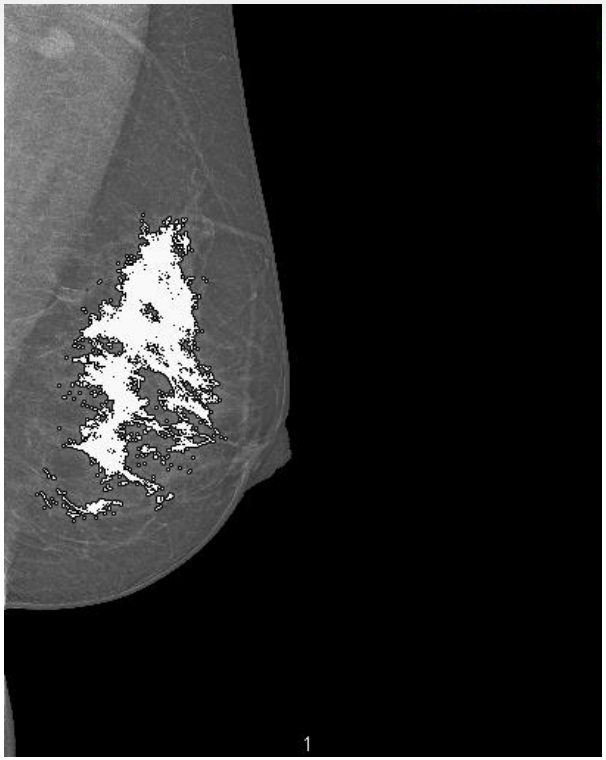
- Discontinuation is additionally associated with other treatment such as the use of symptom-relieving drugs (analgesics, sedatives, anti-depressants)

- There is a need for an early marker for therapy response

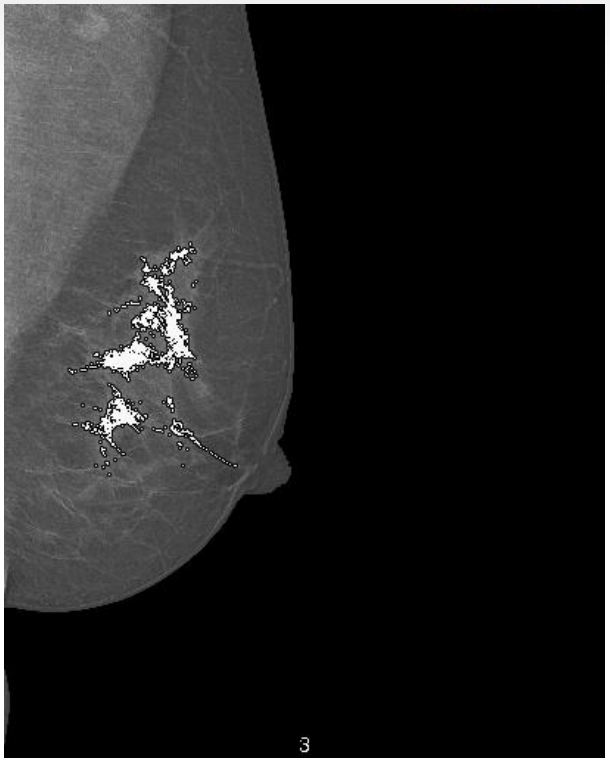


Mammographic density is an early marker of density response. The KARISMA-I trial showed that density decrease already after 6 months of treatment

Before tamoxifen



After 6-months tamoxifen



VOLUME 33 · NUMBER 20 · JULY 10 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Low-Dose Tamoxifen for Mammographic Densi
Reduction: A Randomized Controlled Trial

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KARISMA II, Aim

Investigate if lower doses of tamoxifen are non-inferior in reducing mammographic density compared to the standard dose of tamoxifen, but cause less side-effects

Study population

- 1,440 women aged 40-74 recruited from mammography screening at Södersjukhuset, Stockholm

- Main exclusion criteria were women with cardiovascular disorders and women with almost entirely fatty breasts

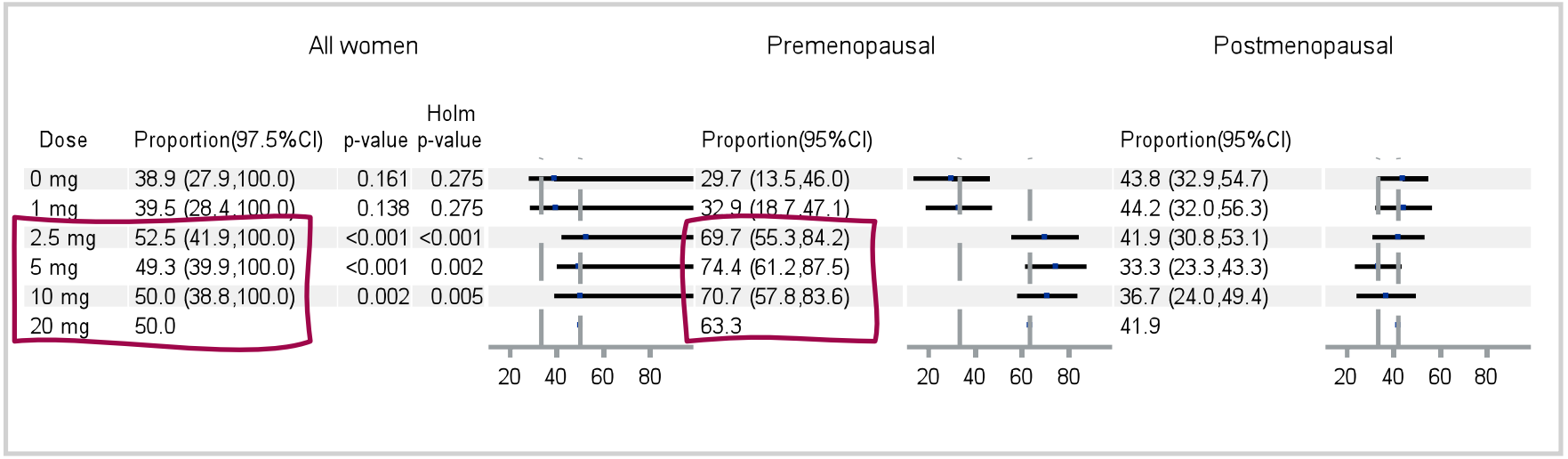
- Intention-to-treat population (N=1,230). Women with two mammogram measurements (at study entry and study exit before or at 6 months)

Methods

- A six-months double-blind randomized placebo-controlled non-inferiority dose-determination phase II trial
- Mammographic density was measured at baseline and at study exit
- Symptom burden was assessed for menopausal similar symptoms (vasomotor, gynaecological, sexual)
- Non-inferiority analysis was performed for mammographic density change
- Prevalence ratios were estimated for symptom burden

Results (1/2) – mammographic density response

The proportions of density responders to lower doses of tamoxifen (2.5 mg, 5 mg, and 10 mg) were non-inferior to the proportion density responders in standard 20 mg dose. Results were confined to premenopausal women.

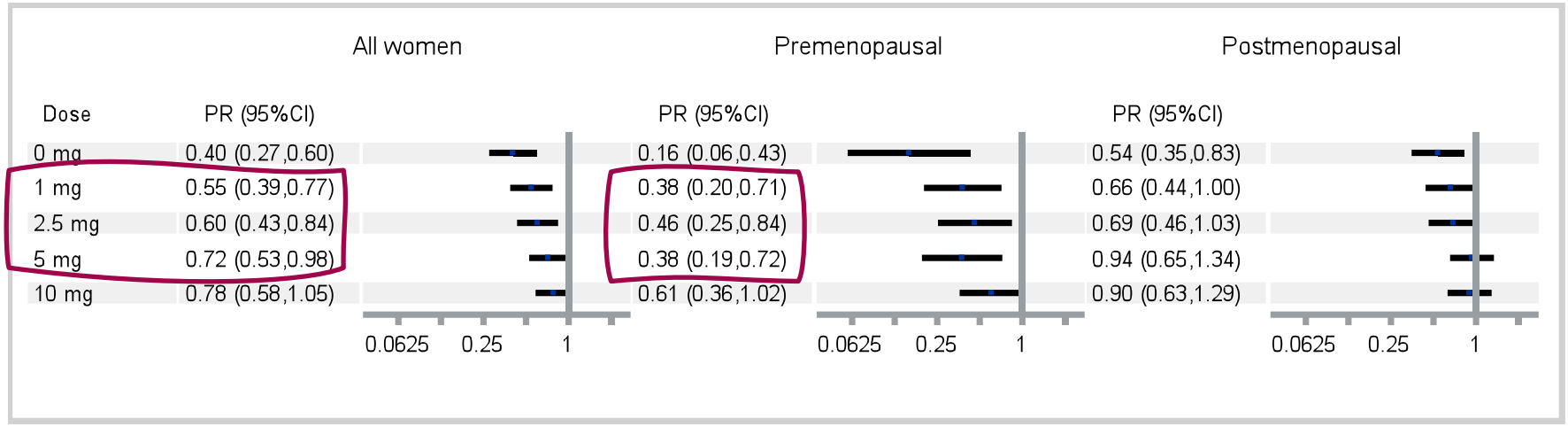


Short-dashed line: Proportion of responders in reference 20 mg arm
Long-dashed line: Non-inferiority margin (33% or fewer responders)

Results (2/2) – severe side-effects reduction

Severe vasomotor side-effects were reduced by ~50% in premenopausal women in doses 1 mg, 2.5 mg, 5 mg compared with standard 20 mg dose

A. Vasomotor severe events (hot flashes, cold sweats, night sweats)



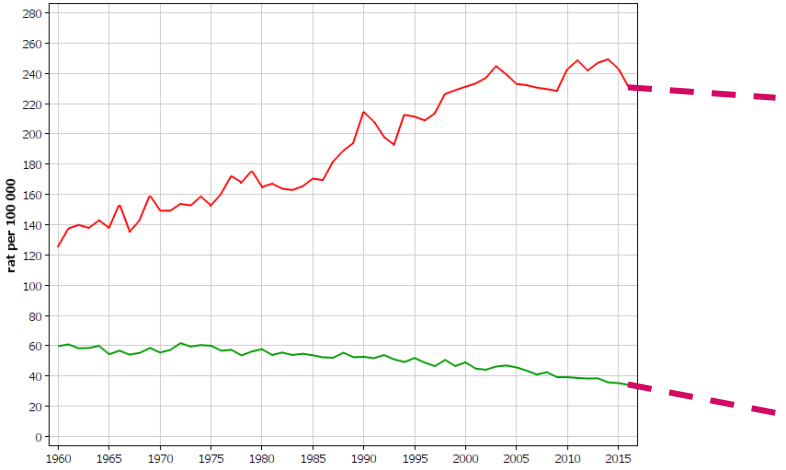
Vertical line: Proportion of severe vasomotor symptoms in 20 mg reference arm

So, can low-dose tamoxifen be used for prevention?

- Approximately 30% of the estrogen-positive invasive cancers can be prevented using tamoxifen for 5 years
- Among women who respond with >10% density decrease within 1.5 years, a ~60% decrease in incidence has been observed during 8-year of follow-up
- Approximately 50% of the women discontinue tamoxifen medication within 5-year of treatment using full dose
- Low-dose tamoxifen (5 mg) reduces recurrence of intraepithelial cancers by ~50% and reduces severe side-effects
- In premenopausal women, low-dose tamoxifen (2.5 mg) reduces mammographic density efficient within 6-months of treatment, an early marker for therapy response to tamoxifen. Severe vaso-motor side-effects were reduced by 50%.
- **A prospective study is needed to test the uptake of low-dose tamoxifen in the population and its effect on reducing breast cancer incidence**

Overall conclusion

- Improved earlier detection of cancers in women who are sent home with a negative mammogram could reduce breast cancer mortality further through individualized screening intervention
- Women using low-dose tamoxifen and show a decrease of mammographic density may show increased tolerability and a reduction in breast cancer incidence



How does the future look like?

- 3D risk is coming
- Currently, a risk model is finalizing for use with tomosynthesis mammography machines.
  Early adopters starts evaluation in August 2021.

- Prevention moves forward
- Study on uptake and efficacy in the population, next step
- Alternatives to low-dose tamoxifen with even lower side-effects?

Acknowledgements

Per Hall, Karolinska Institutet

Kamila Czene, Karolinska Institutet

Researchers, study personnel, study participants in KARMA, KARISMA, LIBRO1, CAHRES, MBTST, CSAW

Märit & Hans Rausing Initiative Against Breast Cancer,
Swedish Medical Research Council,
Swedish Cancer Foundation,
Stockholm County Council,
Kamprad Foundation

Two pending patents with an option to license to iCAD and Atossa