ESMO DEEP DIVE:
BREAST CANCER

BREAKTHROUGHS IN PERSONALISED, MOLECULARLY-INFORMED RISK PREDICTION, SCREENING AND EARLY DETECTION OF BREAST CANCER

Nadia Harbeck, *Chair*

LMU University Hospital, Munich, Germany

ESMO WEBINAR SERIES

PROGRAMME AND SPEAKERS

5 June 2024

5 min	**Welcome and introduction** Nadia Harbeck
25 min	**Screening for breast cancer – what can we do beyond mammography** Tanja Gagliardi
25 min	**Lifestyle changes – is prevention possible?** Suzette Delaloge
25 min	**Emerging data on: How to deal with hereditary risk** Shani Paluch-Shimon
15 min	**LIVE Discussion and Q&A** All

Nadia Harbeck
Chair
LMU University Hospital, Munich

Tanja Gagliardi
Speaker
Royal Marsden Hospital

Shani Paluch-Shimon
Speaker
Hadassah University Hospital

Suzette Delaloge
Speaker
Gustave Roussy, Villejuif

LEARNING OBJECTIVES

- To acquire a deeper understanding of the clinical course of breast cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for breast cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO DEEP DIVE: BREAST CANCER

THANK YOU FOR YOUR ATTENTION

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ESMO DEEP DIVE:
BREAST CANCER

SCREENING FOR BREAST CANCER

What can we do beyond mammography ?

Dr. Tanja Gagliardi

Consultant Radiologist

Royal Marsden Hospital, London, UK

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? SCREENING

Basic characteristics of a screening test - Mammography

- Find disease (BC) when small, not causing symptoms, less likely to have spread beyond the local tumour
- quickly and easily applied
- cost effective (cheap)
- widely available
- detects disease early and reduces ultimately disease related mortality

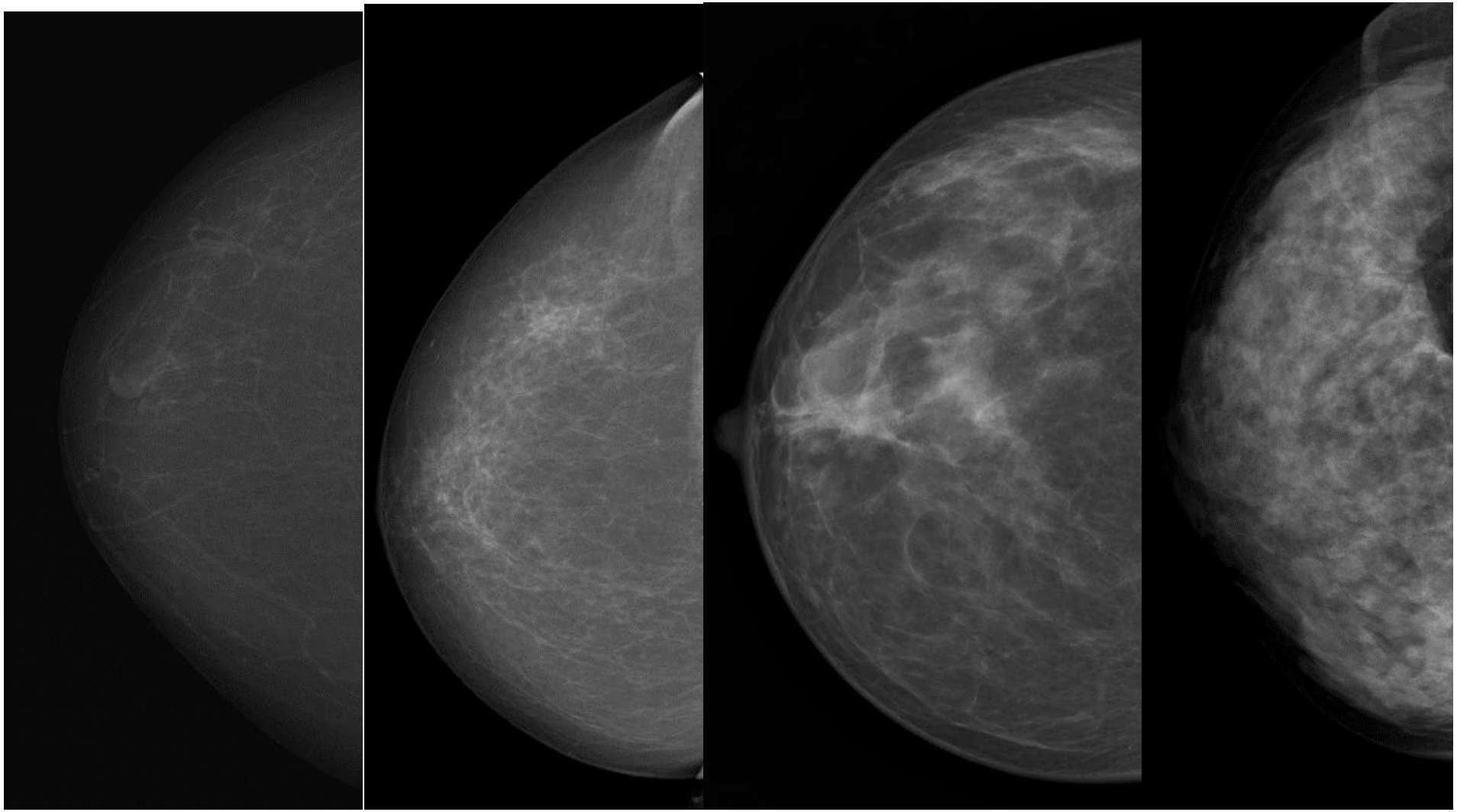
- Mammography
- proven to reduce mortality 20% over last 30 years, **based on age only** and related incidence

- Population Based Screening vs Opportunistic Screening

What has changed ? Why thinking beyond classical screening

- underdiagnosis (breast density), false positive cases (specificity),
- overdiagnosis (lead time bias- DCIS)
- Advances in local and systemic treatment made BC a story of success with
- Nonetheless treatment options are less favourable in advanced disease stages making early detection important

Underdiagnosis/ false positive cases- breast density

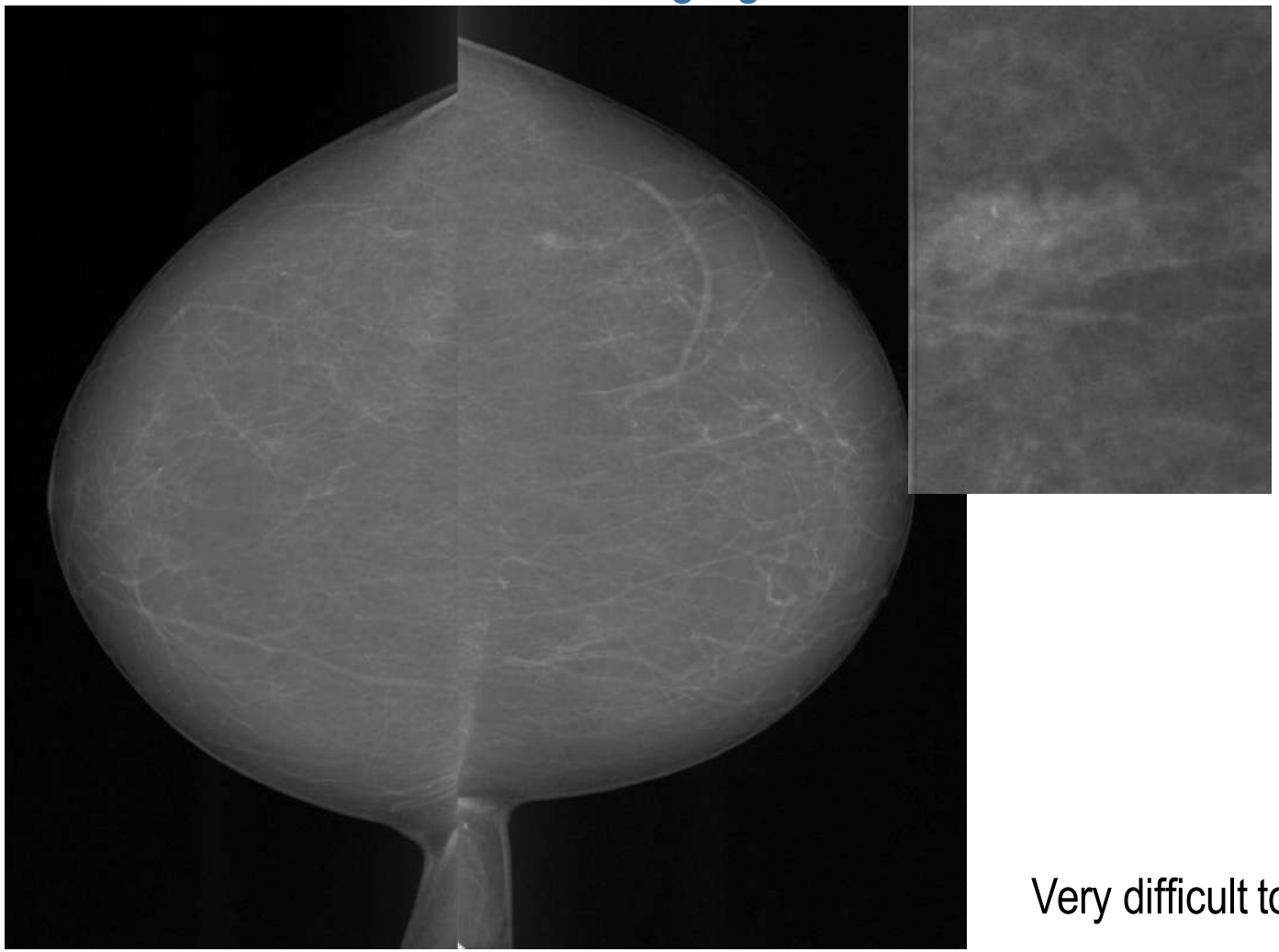


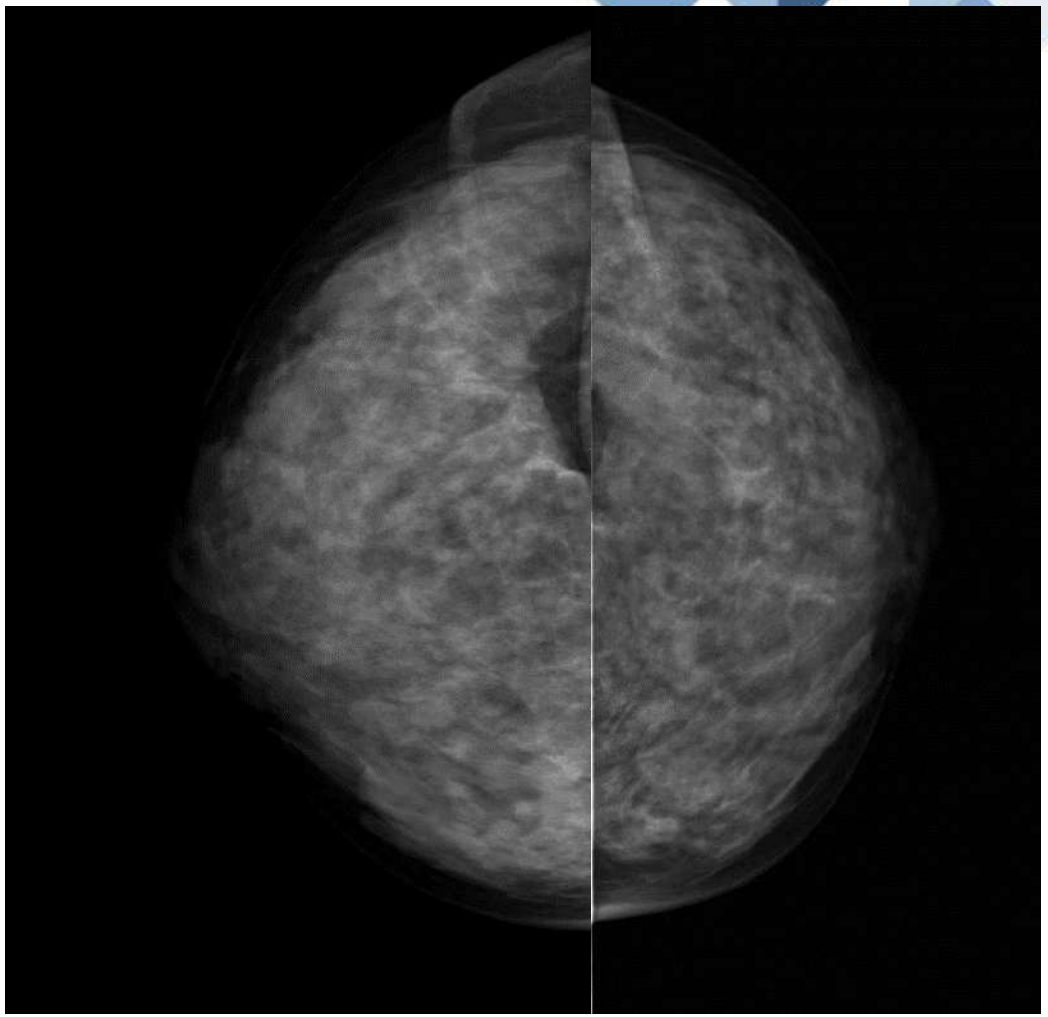
ACR A ACR B ACR C ACR D

A,B: non dense
C,D: dense

DENSITY OF THE BREAST

and related difficulties for imaging





Very difficult to spot a small cancer in a dense breast

BREAST DENSITY

Breast Density Notification Law in 2009 in Connecticut/ FDA finalised language in 3/23

Case of Dr. Nancy Cappello , diagnosed with lymphnode positive BC at age 51 (2004)

- despite regular ,yearly screening mammograms from the age of 40
- regular, monthly self examination, healthy life style, no family history
- Palpable ridge: US revealed 2.5 cm mass, with 13 positive lymphnodes, Stage III c, died of complication related to myelodysplastic syndrome in 2019

Mrs. Cappello campaigned for a law to have patients informed of their breast density and related low diagnostic performance

- low sensitivity of mammography (up to 93% in fatty breast to 30 % in extremely dense breasts (D category)
- Number of false positive results in fatty breast 11/1000 mammo increases to 24/1000 in dense breast
- Screening reduces relative risk of death from BC in fatty breast to 43 % compared to 13 %
- Density is independent risk factor for developing breast cancer aside age and genetics (4-6 fold in D breasts)

Boyd NF et al. Mammographic density and the risk and detection of breast cancer . **N Engl J Med** 2007

van der Waal D, Ripping TM, Verbeek AL, Broeders MJ. Breast cancer screening effect across breast density strata: A case-control study. **Int J Cancer** 2017;140(1):41–49

Brown AL et al Breast Cancer in Dense Breasts: Detection Challenges and Supplemental Screening Opportunities. *Radiographics, Vol 42, Nr 10*

OVERVIEW

Screening for breast cancer-what to do beyond mammography ?

- Clinical Examination
- Diagnostic Imaging modalities
  - 2D mammography – working horse
  - Ultrasound - complimentary tool, primary diagnostic tool in young women
  - Tomosynthesis – address breast density
  - MRI Breast (abbreviated protocol)
  - Contrast enhanced mammography CESM – alternative to MRI- visualises neovascularisation

- Risk stratification vs One-size fits all
  - Risk profile based approach requires patient engagement/choice
  - Improve benefit-to-harm-ratio and cost-effectiveness

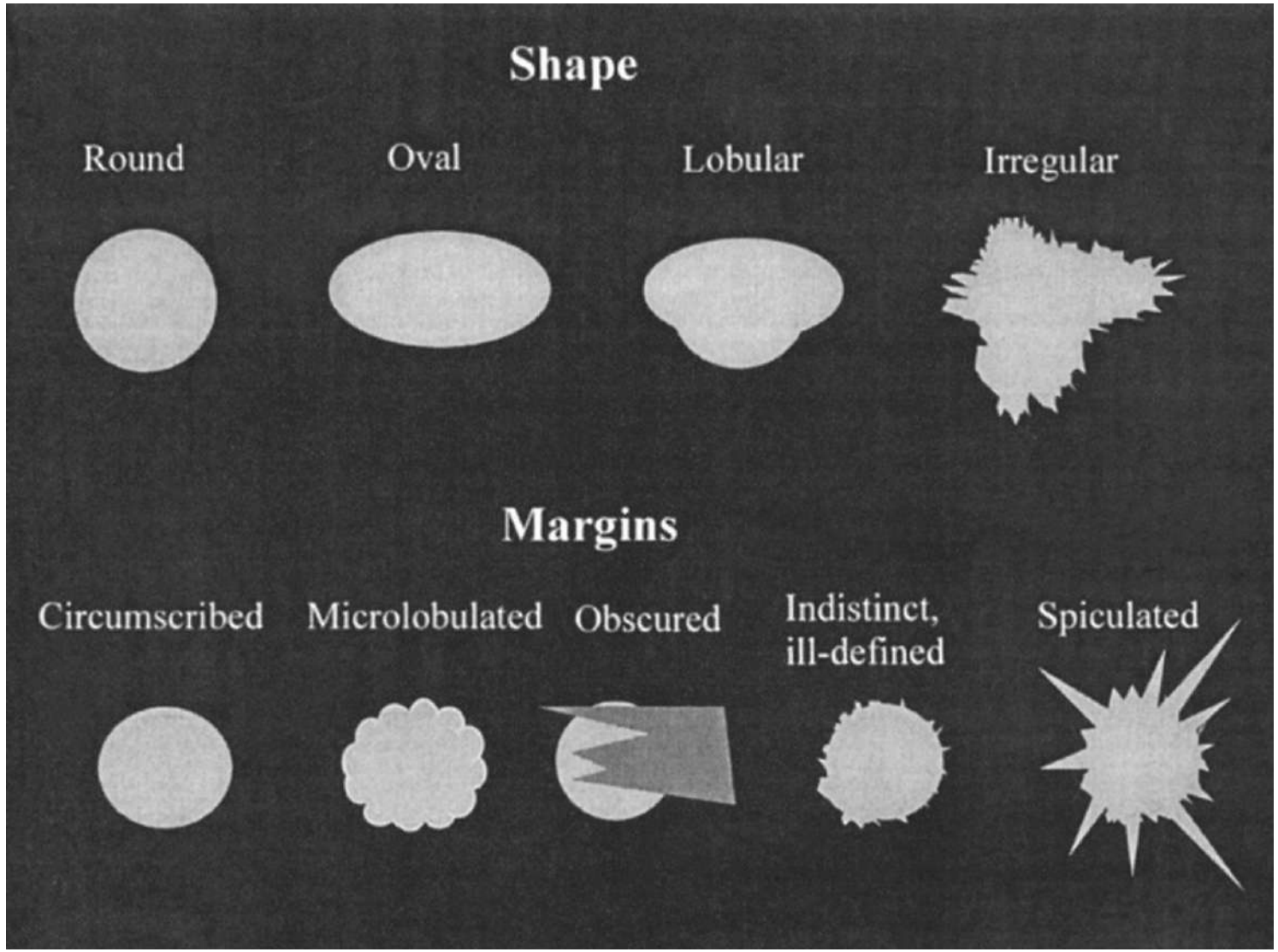
DIAGNOSTIC ASSESSMENT OF BREAST CANCER
CLINICAL EXAMINATION

Diagnostic Performance in 258 Lesions (177 Malignancies, 81 Benign Lesions)

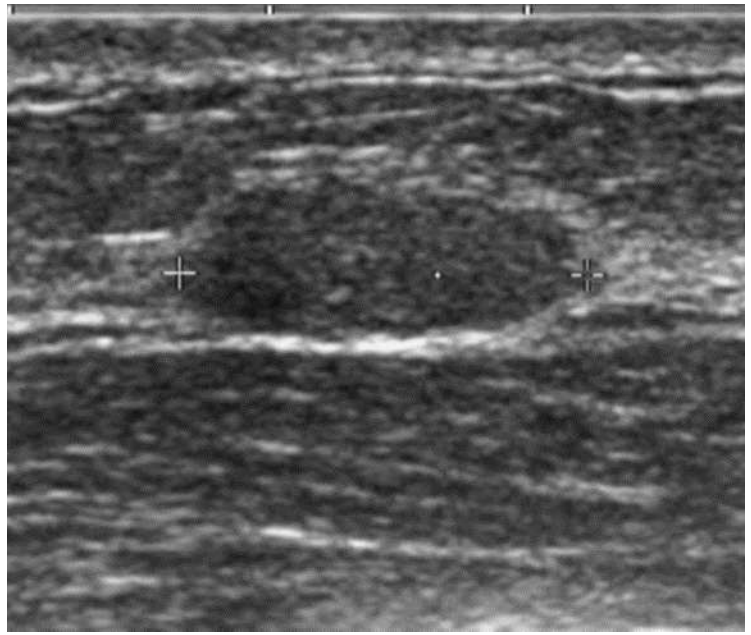
Modality	Sensitivity	Specificity
Mammography	120/177 (67.8)	61/81 (75)
Mammography & Clinical Examination	137/177 (77.4)	58/81 (72)
Clinical Examination	89/177 (50.3)	75/81 (92)
US	147/177 (83.0)	28/81 (34)
Mammography & US	162/177 (91.5)	19/81 (23)
Mammography, Clinical Examination & US	165/177 (93.2)	18/81 (22)
MR Imaging	167/177 (94.4)	21/81 (26)
Mammography, Clinical Examination & MR	176/177 (99.4)	6/81 (7)

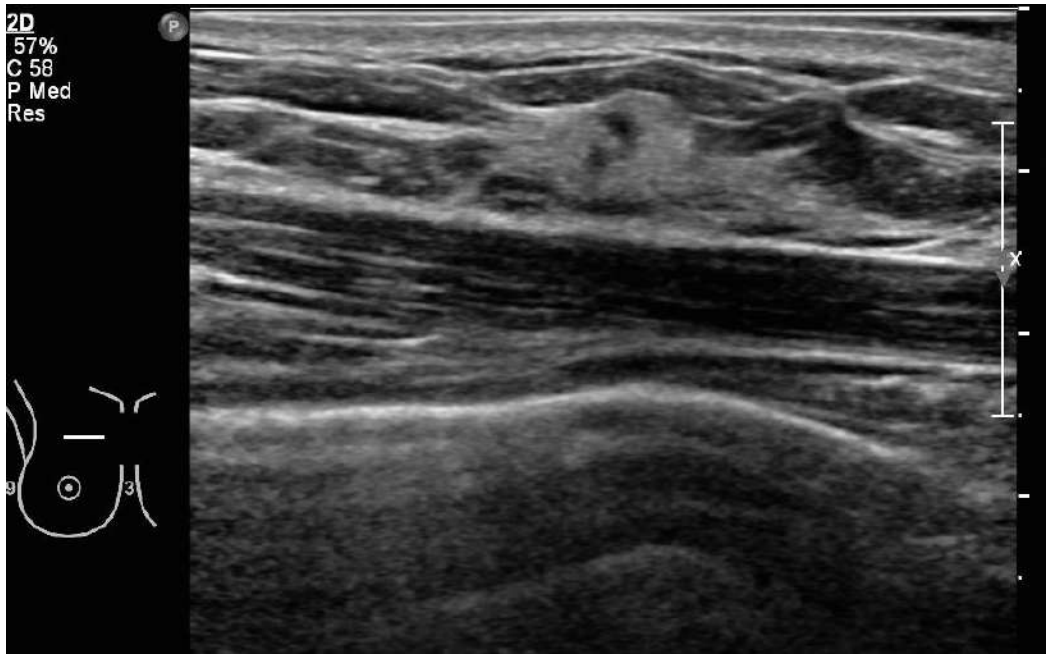
Berg WA et al (2004). **Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative Assessment of breast cancer.** *Radiology 2004*

DIAGNOSTIC IMAGING CHARACTERISTICS



ULTRASOUND AS ADJUNCT TO SCREENING





Fibroadenoma

Invasive ductal carcinoma

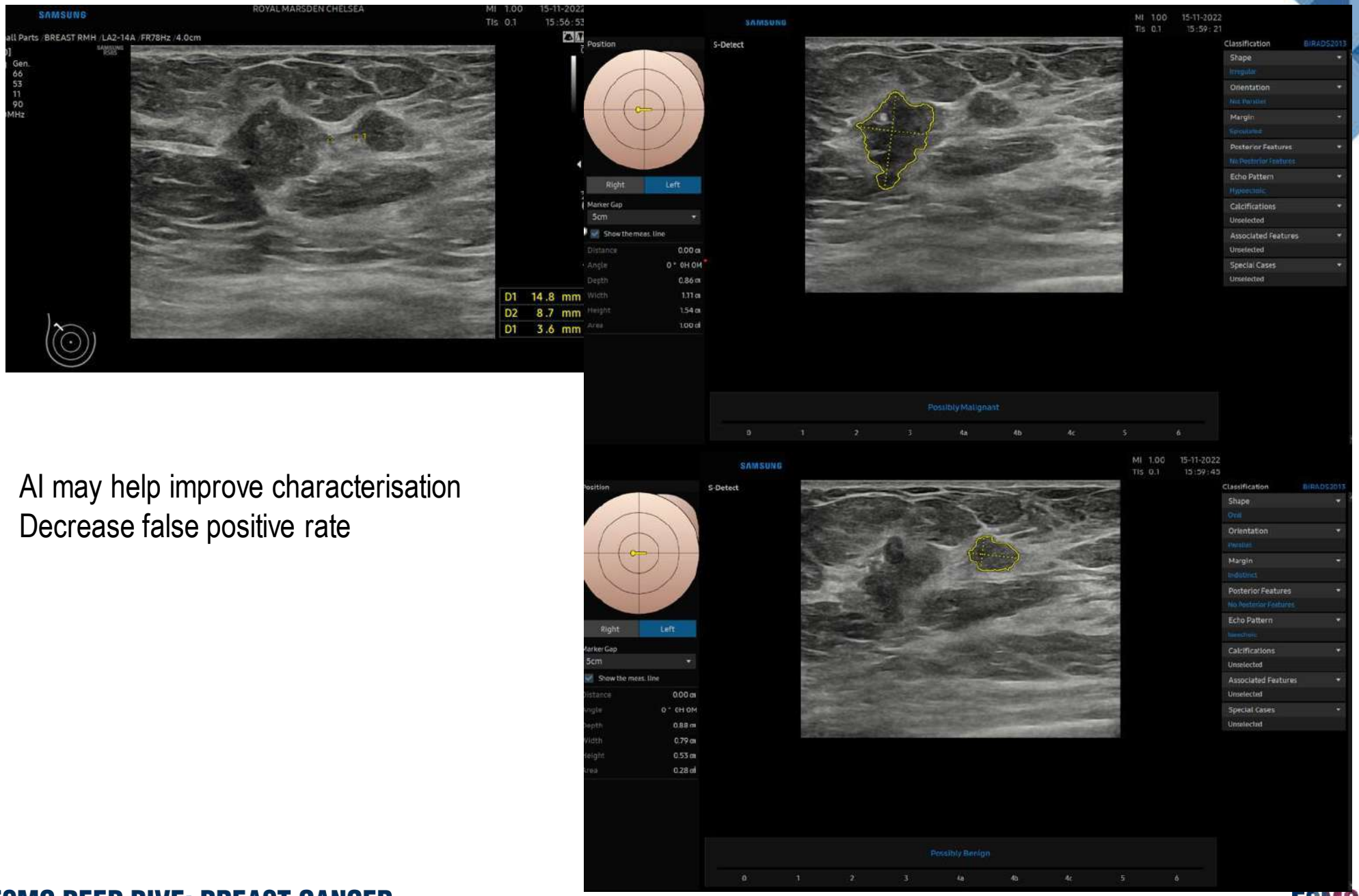
Advantage:

Screening US increases detection of small, node negative cancers not detected on clinical examination and mammogram

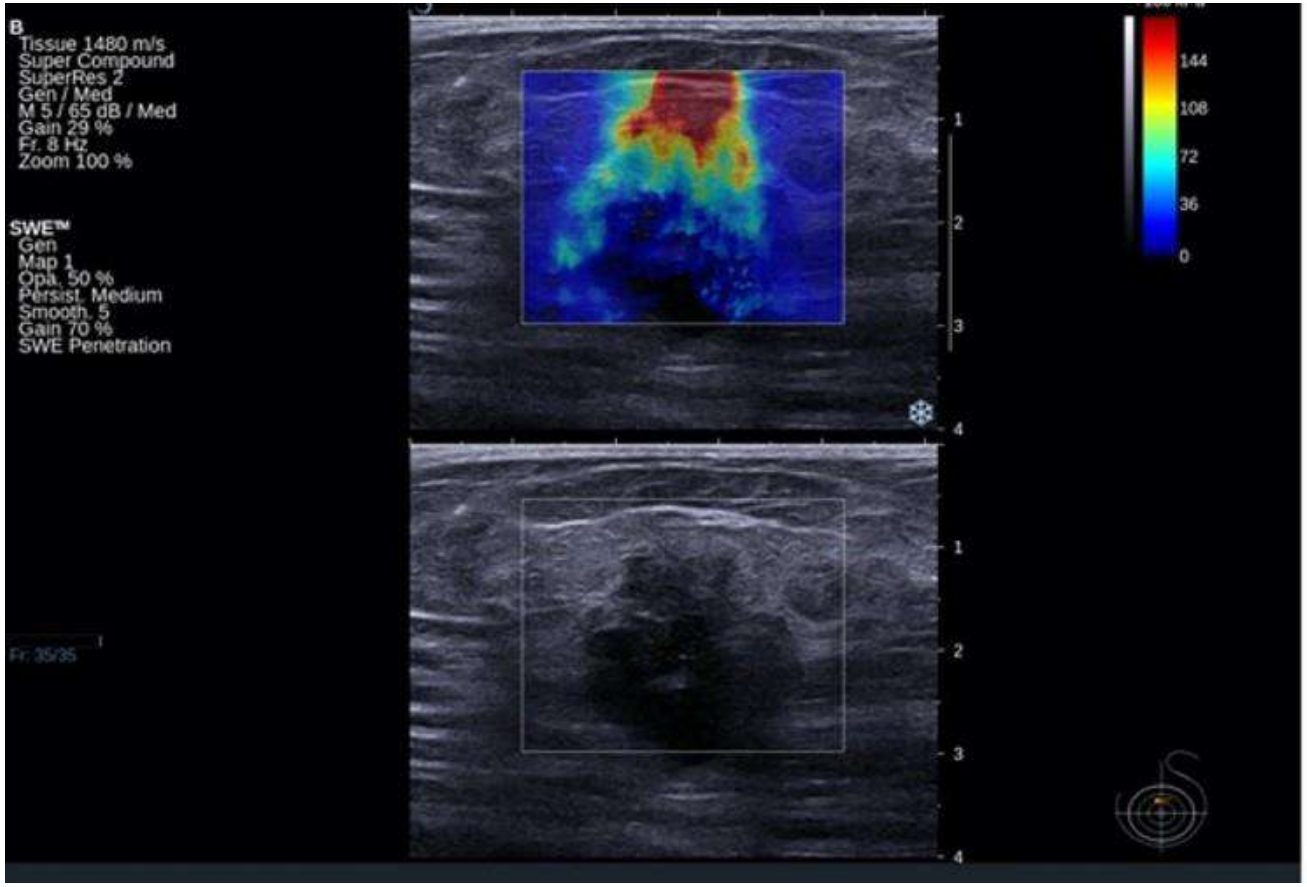
Decreases interval cancer rate

Disadvantage:

Increases false positive rate (134/1000, benchmark mammo 50-120/ 1000) and high negative biopsy rate (not cost effective)



AI may help improve characterisation
Decrease false positive rate



B-mode depicts a hypoechoic inhomogeneous, irregular mass lesion.

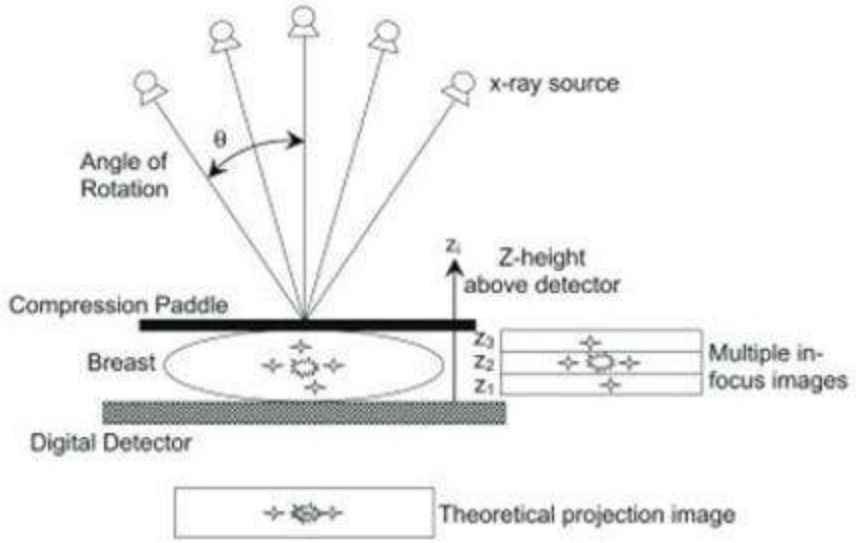
SSI shows a high elasticity score > 140 kpA

Helps avoiding unnecessary, benign BX's

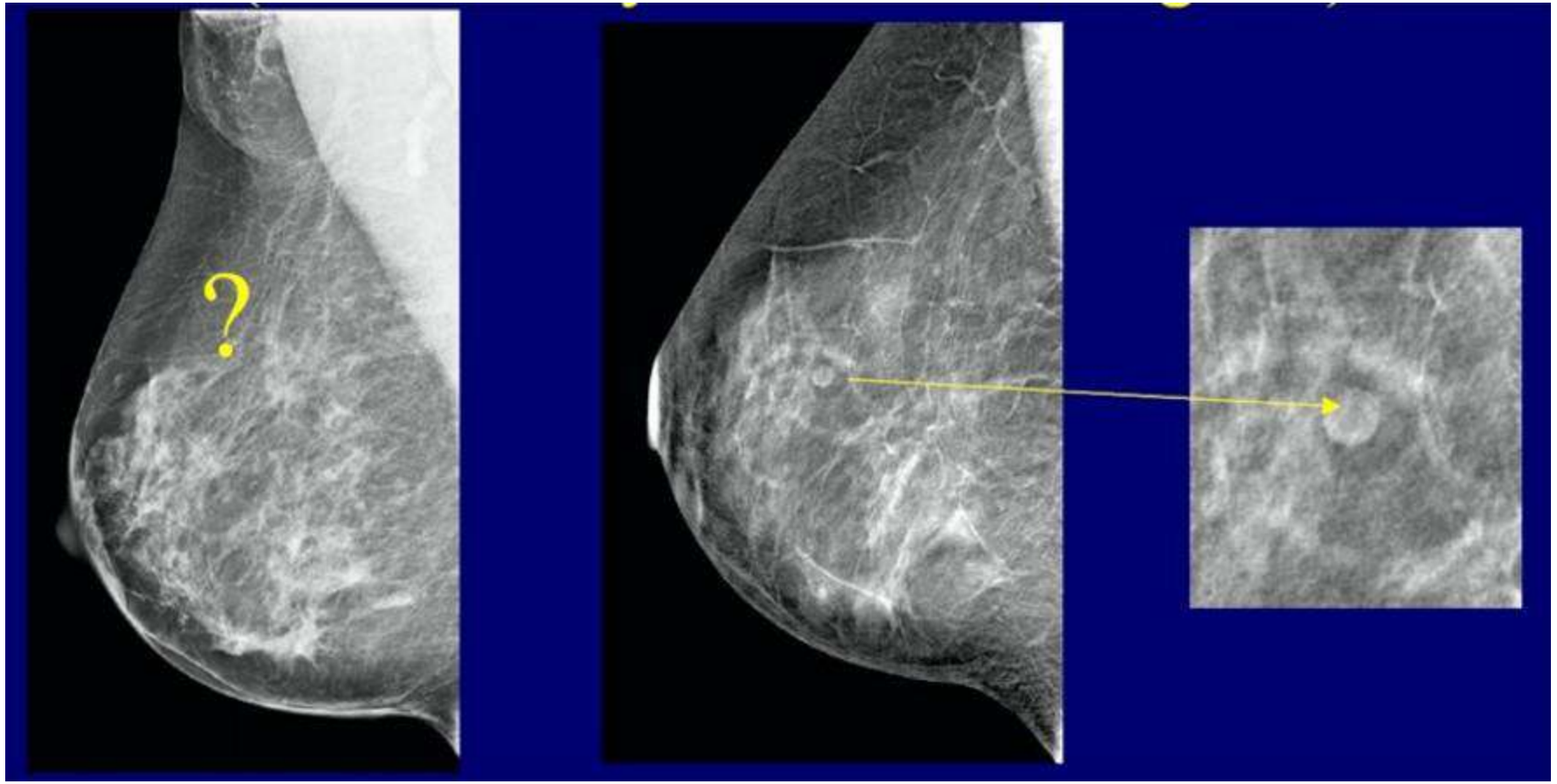
TOMOSYNTHESIS AS ADJUNCT TO SCREENING

The creation of a 3D image of the breast by digital processing of multiple x-ray projection images.

A series of usually 7-9 low-dose images are recorded as the mammographic unit moves gradually in a small arc over the compressed breast.



TOMOSYNTHESIS HELPS MITIGATE DENSITY PROBLEM



- Improved margin assessment
- Improved characterisation
- Reduces recall rates in screening setting
- Increases cancer detection rate
- Increases false positive rate
- **Less effective in very dense D breast**

Gao Y, Moy L, Heller SL. Digital Breast Tomosynthesis: Update on Technology, Evidence, and Clinical Practice. ***RadioGraphics*** *2021;41(2):321–337*

TOMOSYNTHESIS

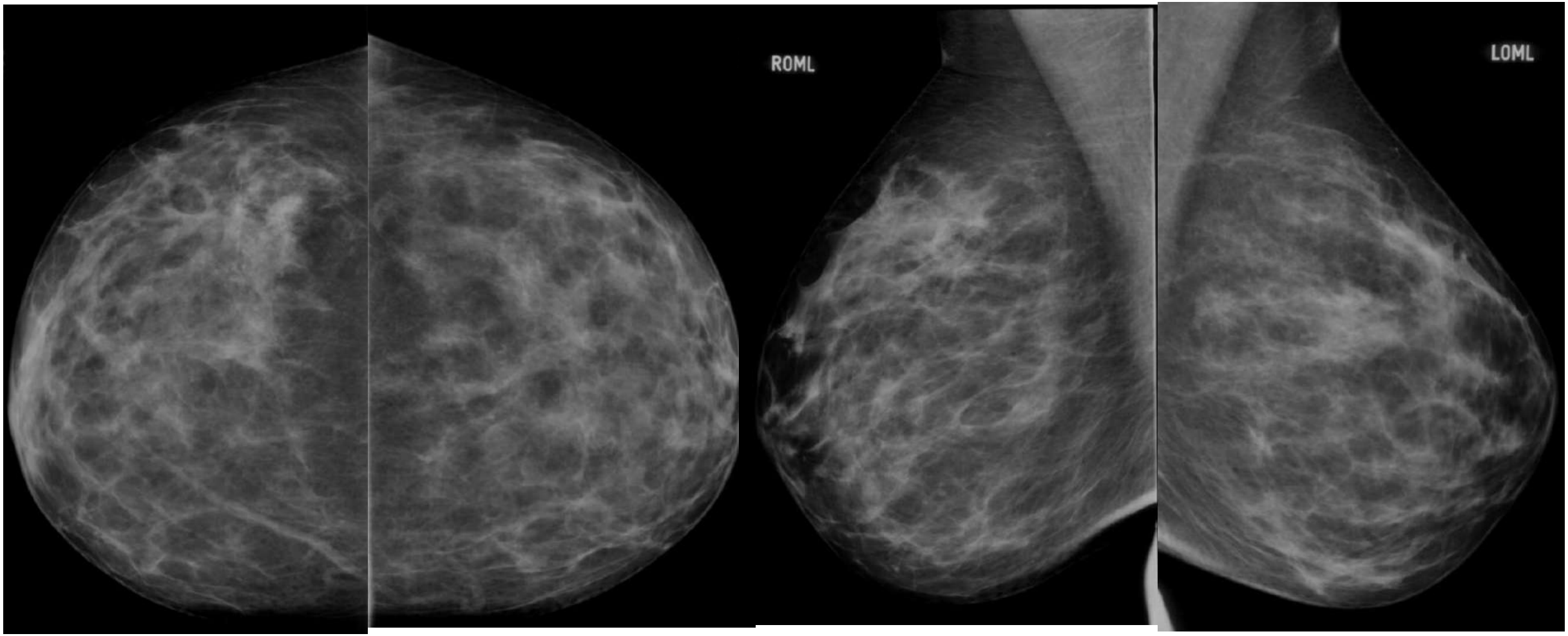
Limitations

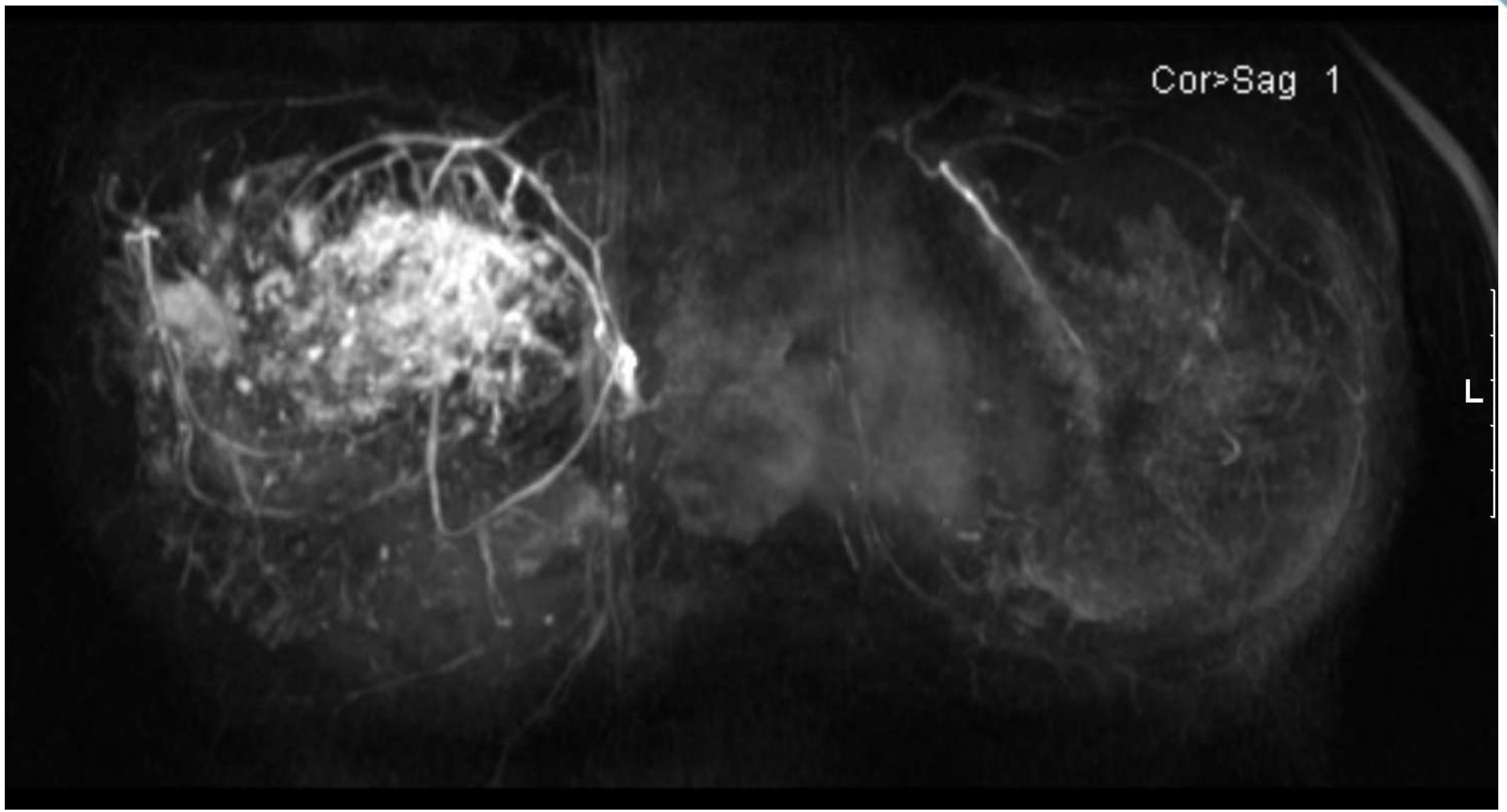
- Slightly increased dose compared to conventional mammography

  (FDA limited dose of 300 millirads per exposure; convent. Mammo: 150 -250 mr)

- Increased reading times
- Increased mass lesion detection (benign/malignant)
- Possibly inferior regarding detection and characterization of microcalcifications

CAN MRI HELP ?





Extensive high grade DCIS

MRI-SCREENING TOOL IN HIGH RISK WOMEN ?

1909 women, lifetime risk greater or equal 15%

	Sensitivity Any Breast Cancer	Invasive BC	Specificity
Clinical breast examination	17,8	17,9	98,1
Mammography	40,0	33,3	95
MRI	71,1	79,5	89,8

Kriege M et al. Efficacy of MRI and mammography for breast-cancer screening in women with a fimilial or genetic predisposition. N Engl J Med 2004

RISK REDUCTION AND SCREENING OF CANCER IN HEREDITARY BREAST-OVARIAN CANCER SYNDROMES

ESMO Clinical Practice Guideline

BRCA 1

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

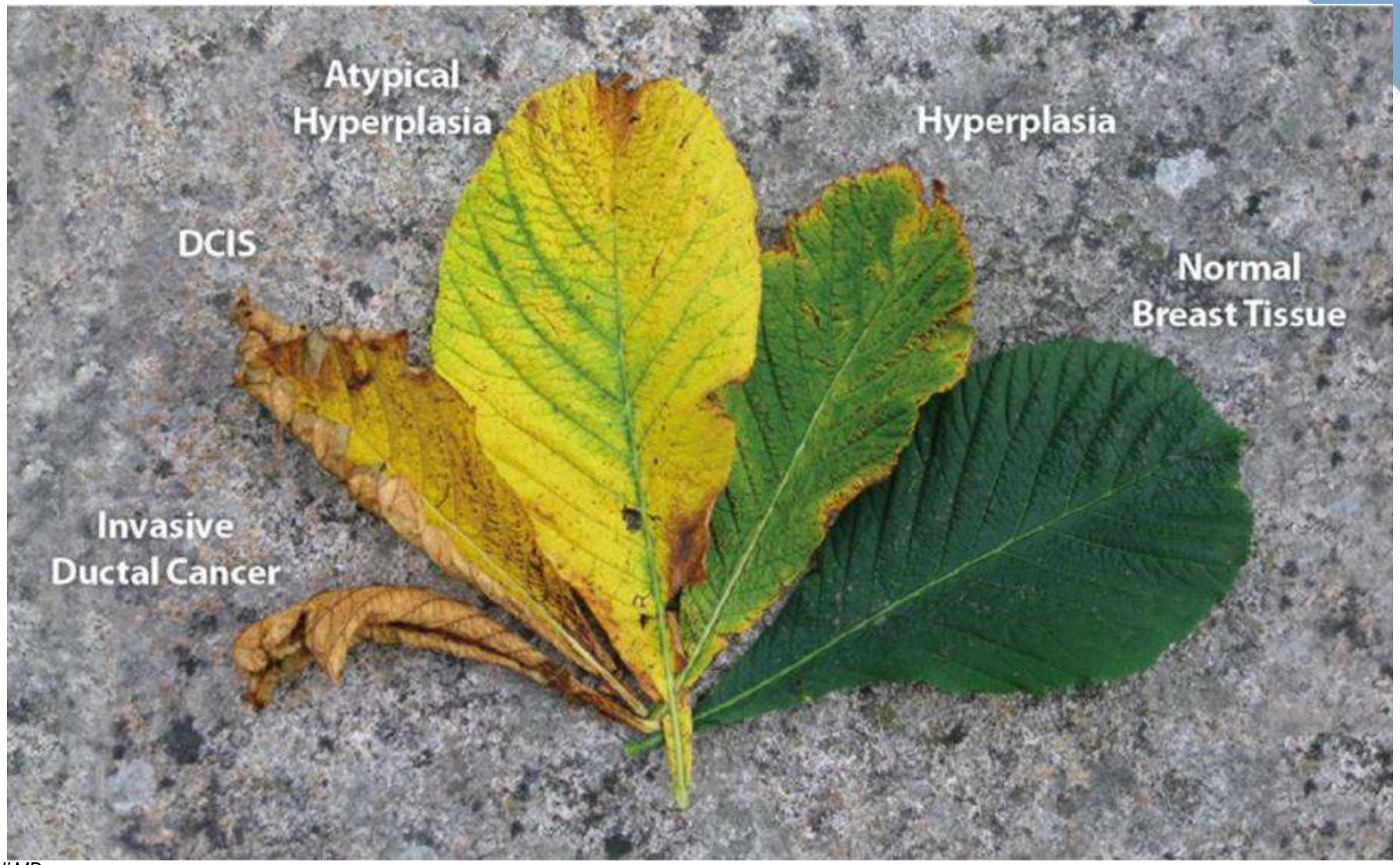
BRCA 2

Intensified surveillance with MRI from age 30 or 5 years younger than the youngest family member with BC [A]

Imaging should be performed annually [A]

-no data on cessation date of MRI
-as long as women is in good health
-not recommended to “switch” to mammography once density decreases with age

Ann Oncol. 2023;34(1):33-47. C. Sessa, J. Balmaña, S.L. Bober, et al, on behalf of the ESMO Guidelines Committee



Tanja Gagliardi MD

- High sensitivity but moderate specificity
  - True positive : false positive = 1.9 : 1
- Pre-operative MRI changes surgical treatment
  - BCT -> MX
- Delays treatment (sec. look ultrasound, BX, MRI guided BX)
- Costly and time consuming (? Abbreviated MRI)
- No impact on Overall Survival
- Little impact on local recurrent disease

Houssami, N., Turner, R.M. & Morrow, M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat ***165****, 273–283 (2017)*

EUSOBI RECOMMENDATIONS

European Radiology (2022) 32:4036–4045
https://doi.org/10.1007/s00330-022-08617-6

BREAST

Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI)

Ritse M. Mann[1,2] · Alexandra Athanasiou[3] · Pascal A. T. Baltzer[4] · Julia Camps-Herrero[5] · Paola Clauser[4] · Eva M. Fallenberg[6] · Gabor Forrai[7] · Michael H. Fuchsjäger[8] · Thomas H. Helbich[4] · Fleur Killburn-Toppin[9] · Mihai Lesaru[10] · Pietro Panizza[11] · Federica Pediconi[12] · Ruud M. Pijnappel[13,14] · Katja Pinker[4,15] · Francesco Sardanelli[16,17] · Tamar Sella[18] · Isabelle Thomassin-Naggara[19] · Sophia Zackrisson[20] · Fiona J. Gilbert[9] · Christiane K. Kuhl[21] · On behalf of the European Society of Breast Imaging (EUSOBI)

"In light of the available evidence, in women aged 50 to 70 years with extremely dense breasts (8% of screening population), the EUSOBI now recommends offering screening breast MRI every 2 to 4 years "

-Radiology Societies and Policymakers should act on this

- Women should be counselled and informed

OVERVIEW

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  - 2D mammography – working horse
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  - MRI Breast (abbreviated protocol)
  - Contrast enhanced mammography CESM – alternative to MRI- visualises neovascularisation

- Risk stratification vs One-size fits all
  - Risk profile based approach requires patient engagement/choice
  - Improve benefit-to-harm-ratio and cost-effectiveness

WHICH MODALITY IS BETTER FOR BC DIAGNOSIS ?

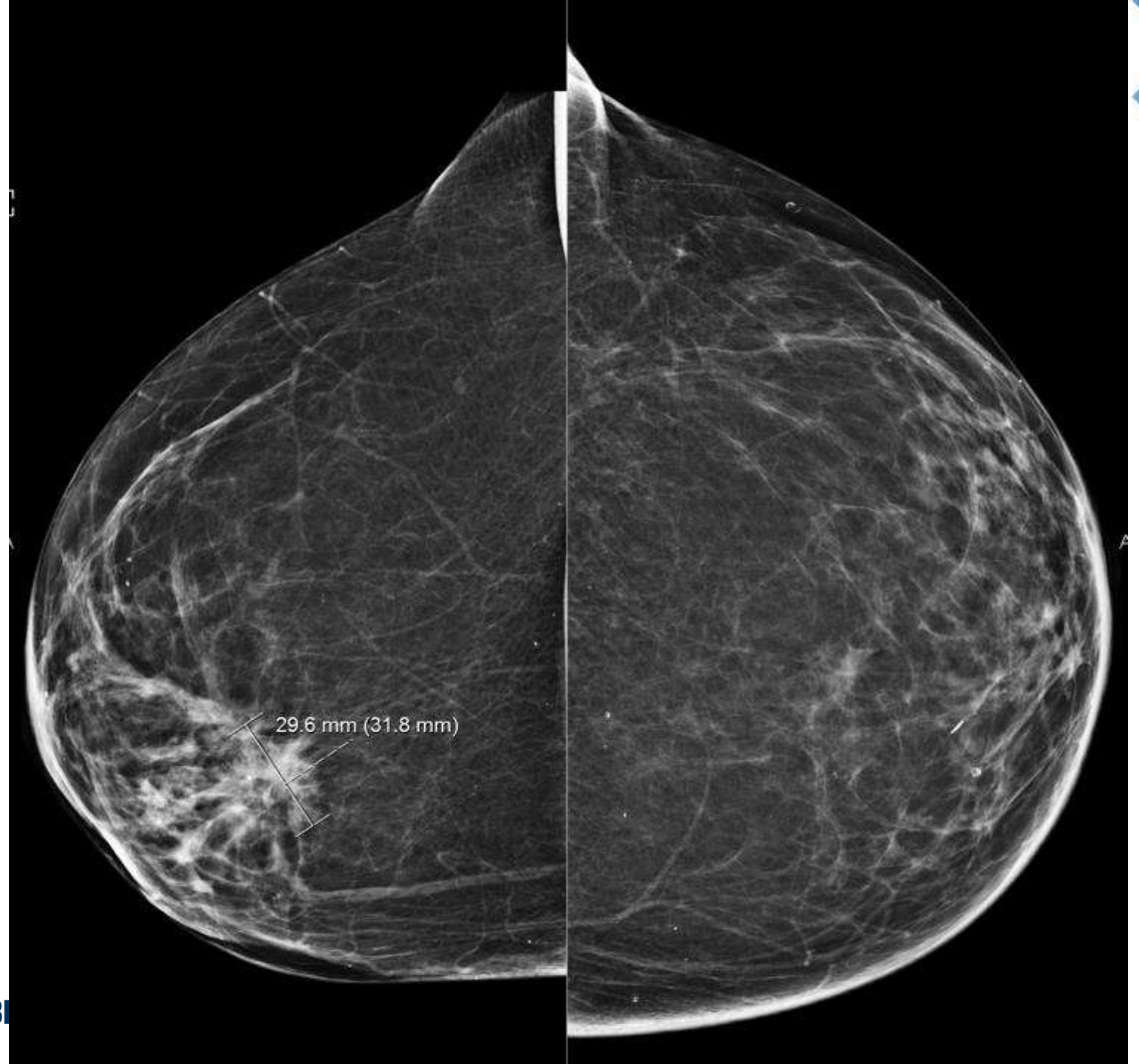
Mammography vs Contrast Enhanced Mammogram VS MRI

Breast MRI introduced in 1984, CEM in 2011 (approved by FDA as adjunct modality for BC diagnostic follow up, but not screening)

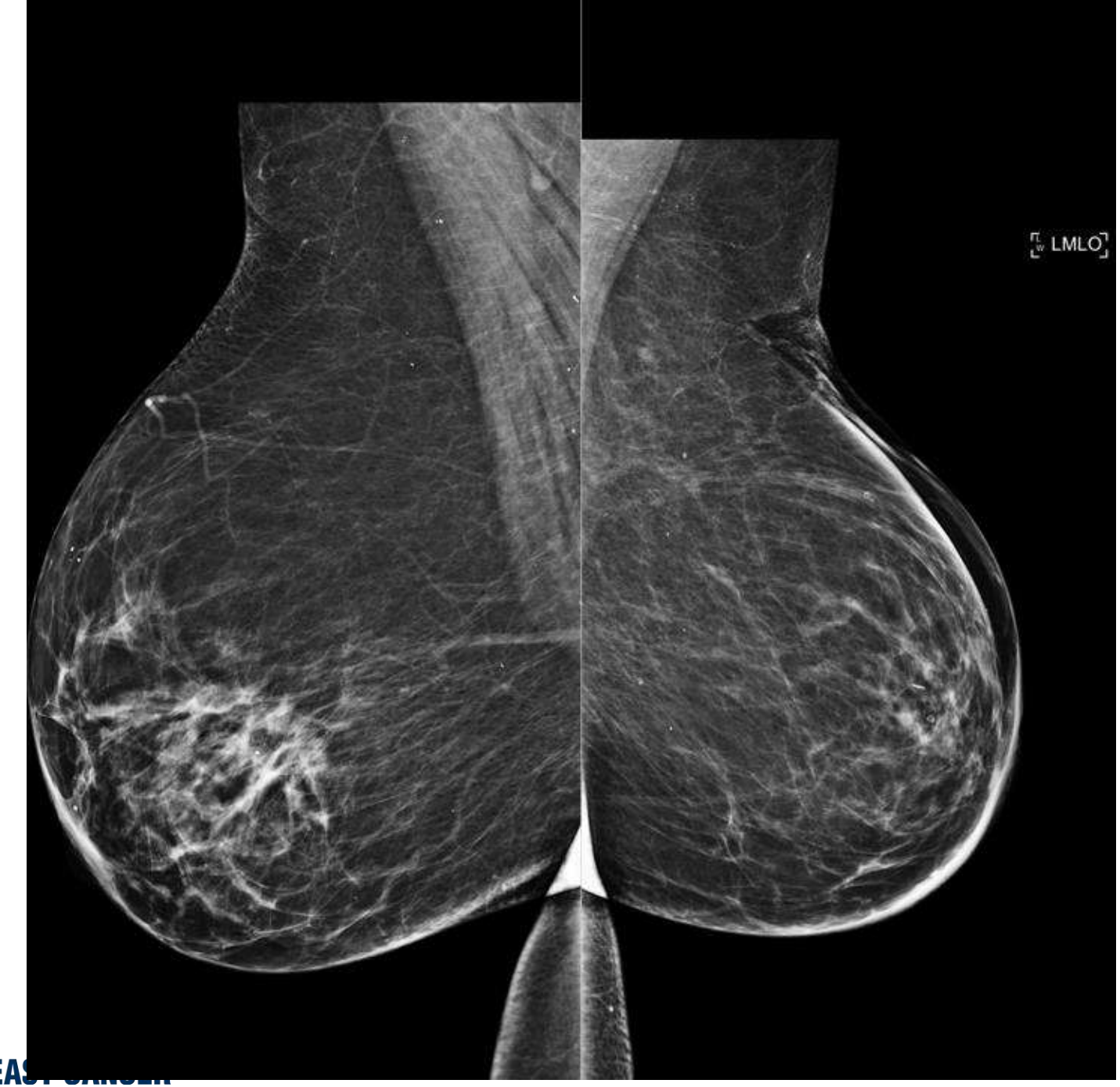
- Mammogram standard for screening and symptomatic services, limitations in dense breast tissue, needs supplemented by Ultrasound
- CEM provides functional information similar to MRI visualising tumour vascularisation

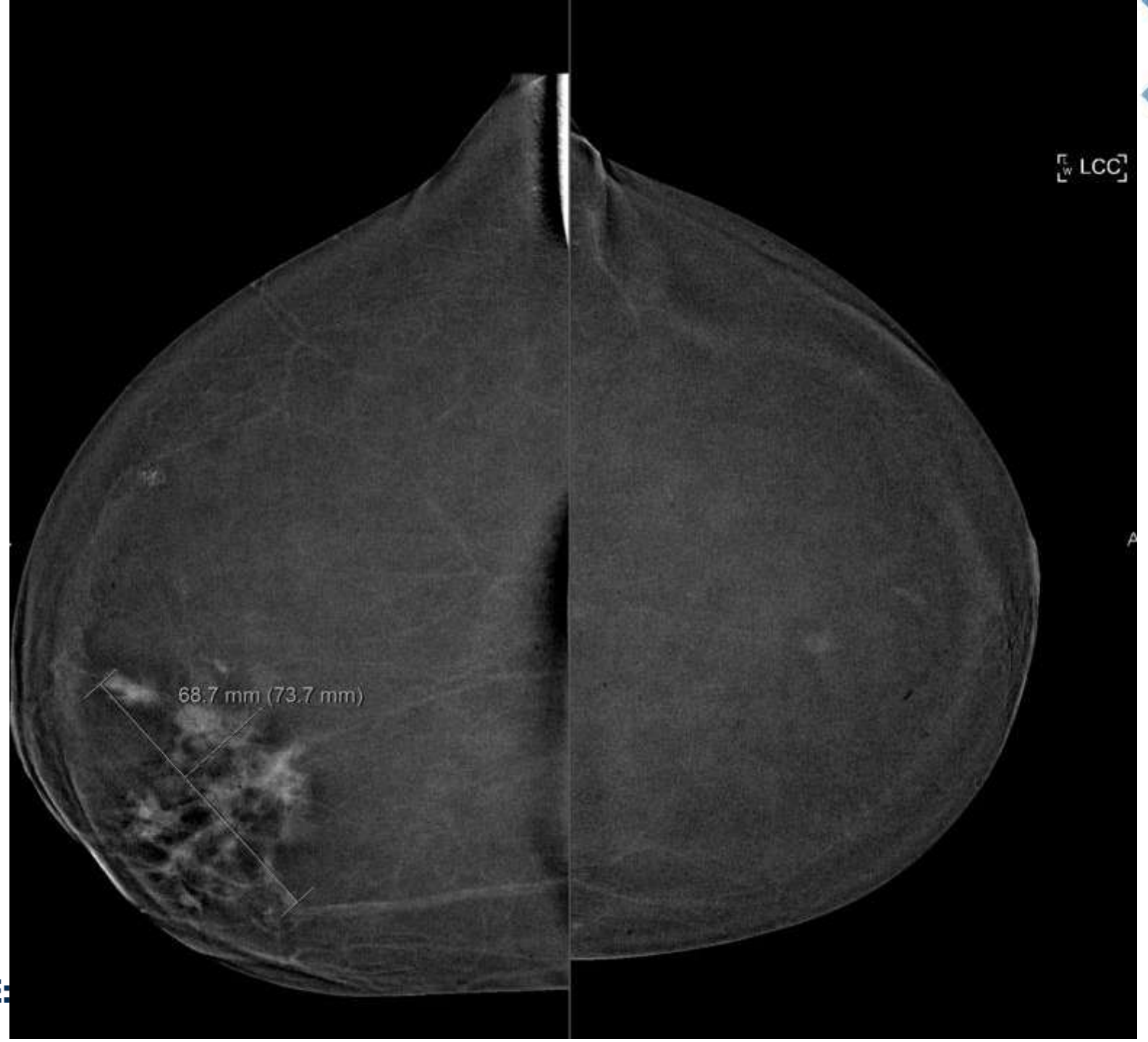
- Sensitivity CEM vs mammography: 90.5% vs 52.4%
- Specificity CEM vs Mammography: 76.1 % vs 90.5%
- MRI Sensitivity up to 100%, Specificity 70-98 %
- MRI covers areas not well seen on mammo/CEM: posterior locations, prepectoral area, axilla
- MRI effective in implant diagnosis, no radiation, chemotheraphy assessment

Invasive
Lobular
Cancer

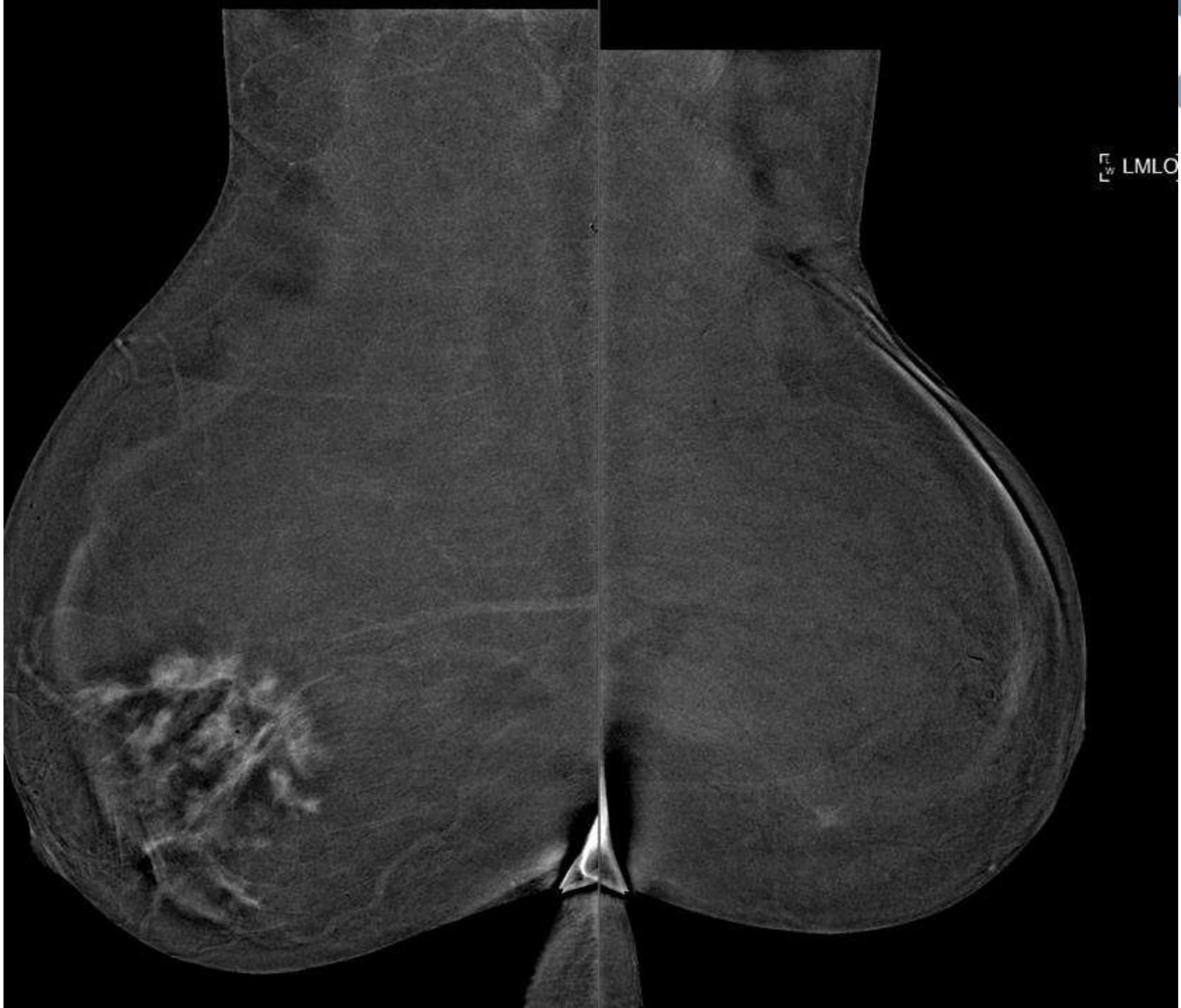


2 D mammography


LMLO



Contrast enhanced
Mammography
CESM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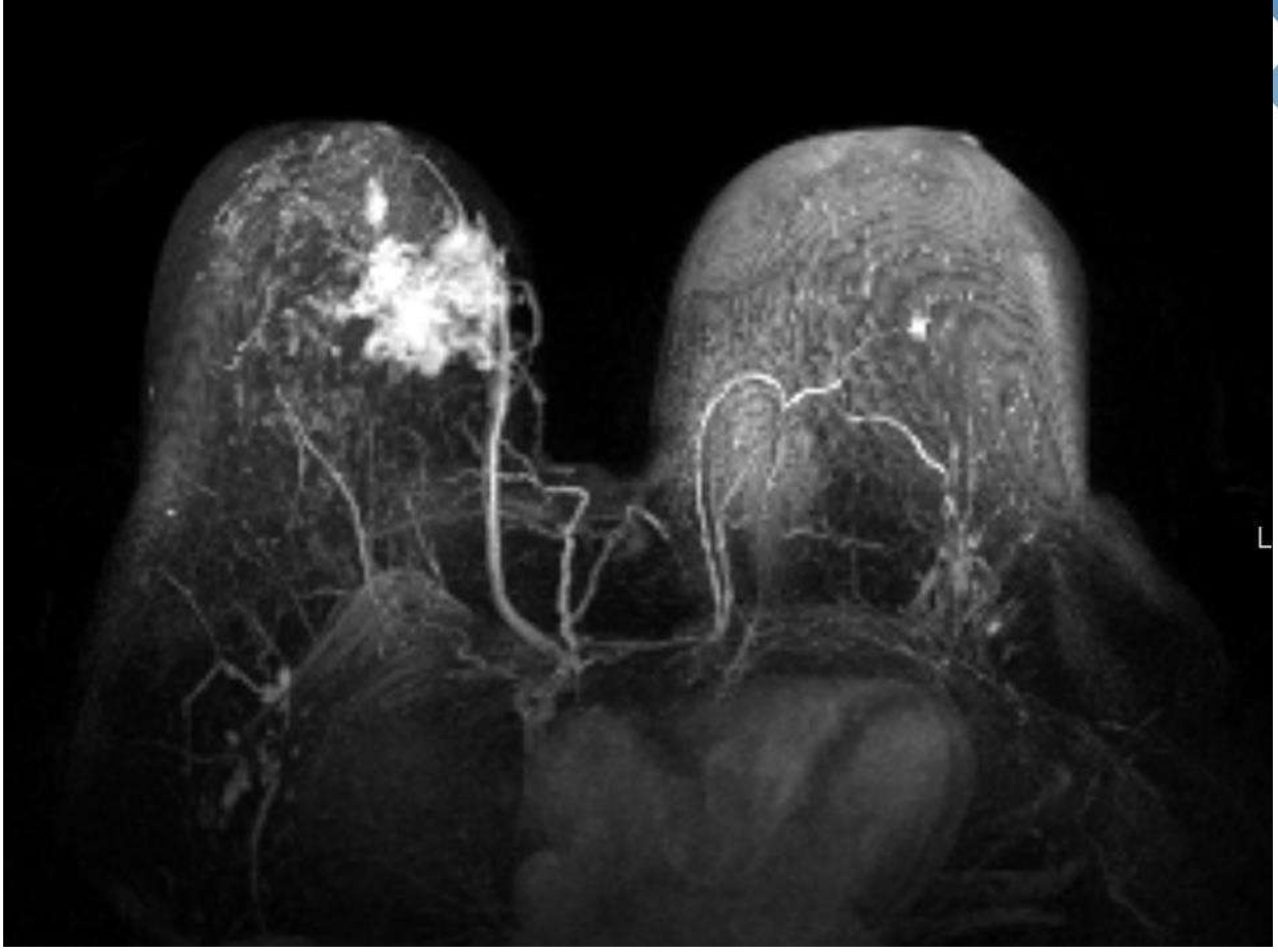
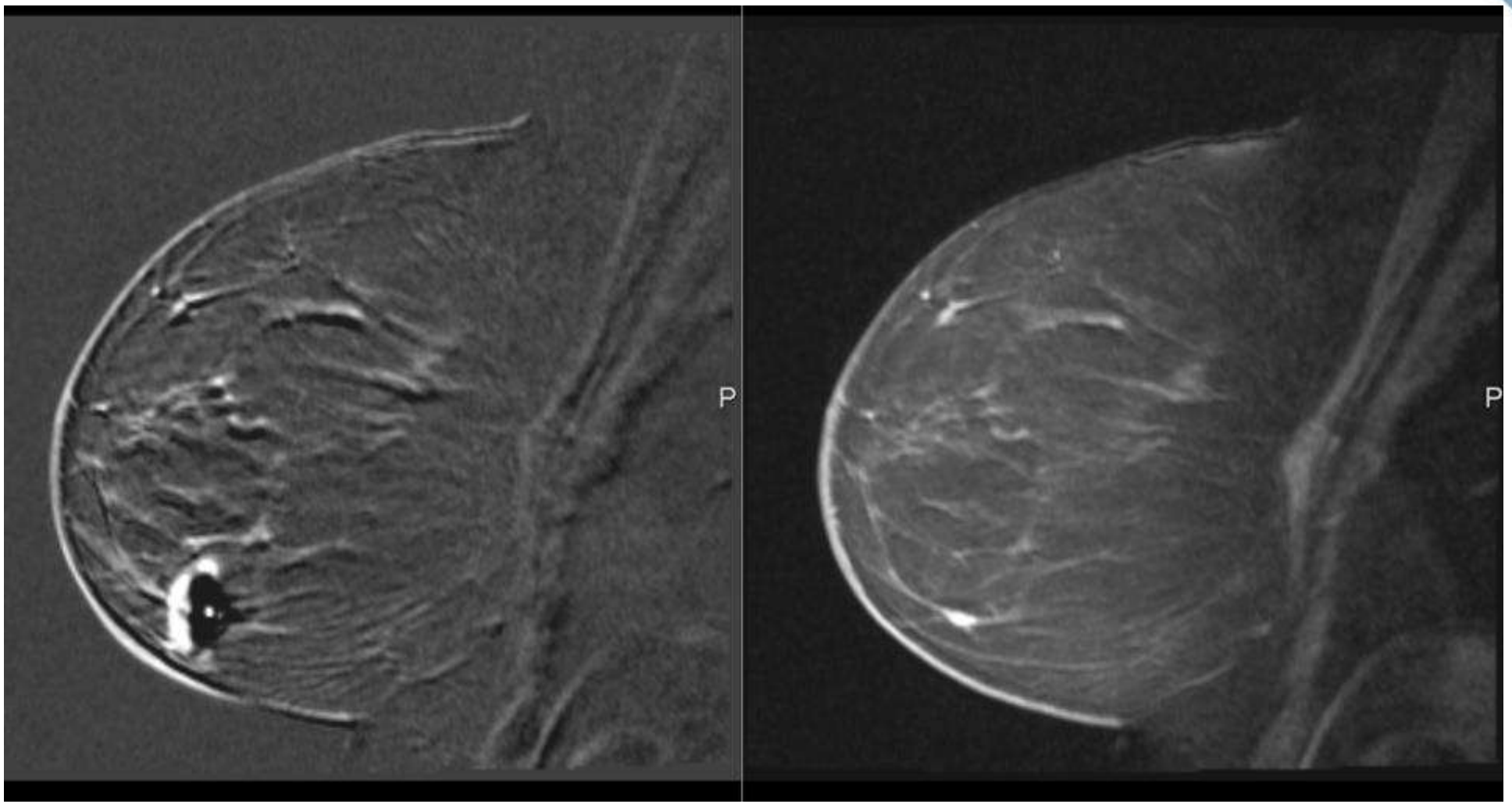


MRI MIP

Contralateral lesion



Invasive lobular cancer bilateral, confirmed via MRI guided BX

CONTRAST ENHANCED MAMMOGRAPHY CESM

Why would you do it ?

- To mitigate low sensitivity of dense breast tissue
- As alternative to MRI breast if no easy access to MRI or MRI guided facilities, contra-indication to MRI
- One –stop – shopping principle (no new date for MRI needed)

Marcon et al. European Radiology
https://doi.org/10.1007/s00330-024-10740-5

European Radiology

INVITED REVIEW Open Access

ESR Essentials: screening for breast cancer - general recommendations by EUSOBI

Magda Marcon[1,2*], Michael H. Fuchsjäger[3], Paola Clauser[4] and Ritse M. Mann[5]

- Regular mammography should be considered mainstay of breast cancer screening NO CHANGE
- High-risk-women and women with extremely dense breast tissue (BI-RADS D) should use MRI for supplemental screening or Ultrasound if MRI is not available
- Women need to participate actively in the decision to undergo personalised screening- risk stratified approach early in life

Eur Radiol. 2024 Apr 24. doi: 10.1007/s00330-024-10740-5.

RISK STRATIFICATION VIA RISK PREDICTION MODELLS

Vs One-size-fits all

- Age of menarche and menopause
- Reproductive history (breast feeding)
- Obesity
- Previous biopsy with atypia

- Previous thoracic radiation therapy (mantle field radiation: age 20- 35 y)
- Family cancer history, Genetic profile (BRCA1/ BRCA2 carrier), Low penetrance genes (CHEK 2,SNP's)

- Breast density (2.9-6 fold increased risk compared to predominantly fatty breasts)

RISK CATEGORIES

Average risk= life time risk of 15 % or less

Intermediate risk= life time risk of 15-20 %

biopsy with atypical ductal hyperplasia (ADH)

biopsy with lobular carcinoma in situ (LCIS)

previous personal history of breast cancer

High risk = life time risk of > 20 %

- intermediate high : highly pos. family history, but no known mutation; CHEK2 or BARD1 (low penetr. mut.)
- very high > 50 % life time risk, due to hereditary mutations in high penetr. genes BRCA1/ BRCA2 (5-10% of all breast cancer cases

ESMO DEEP DIVE:
BREAST CANCER

SCREENING FOR BREAST CANCER

What can we do beyond mammography ?

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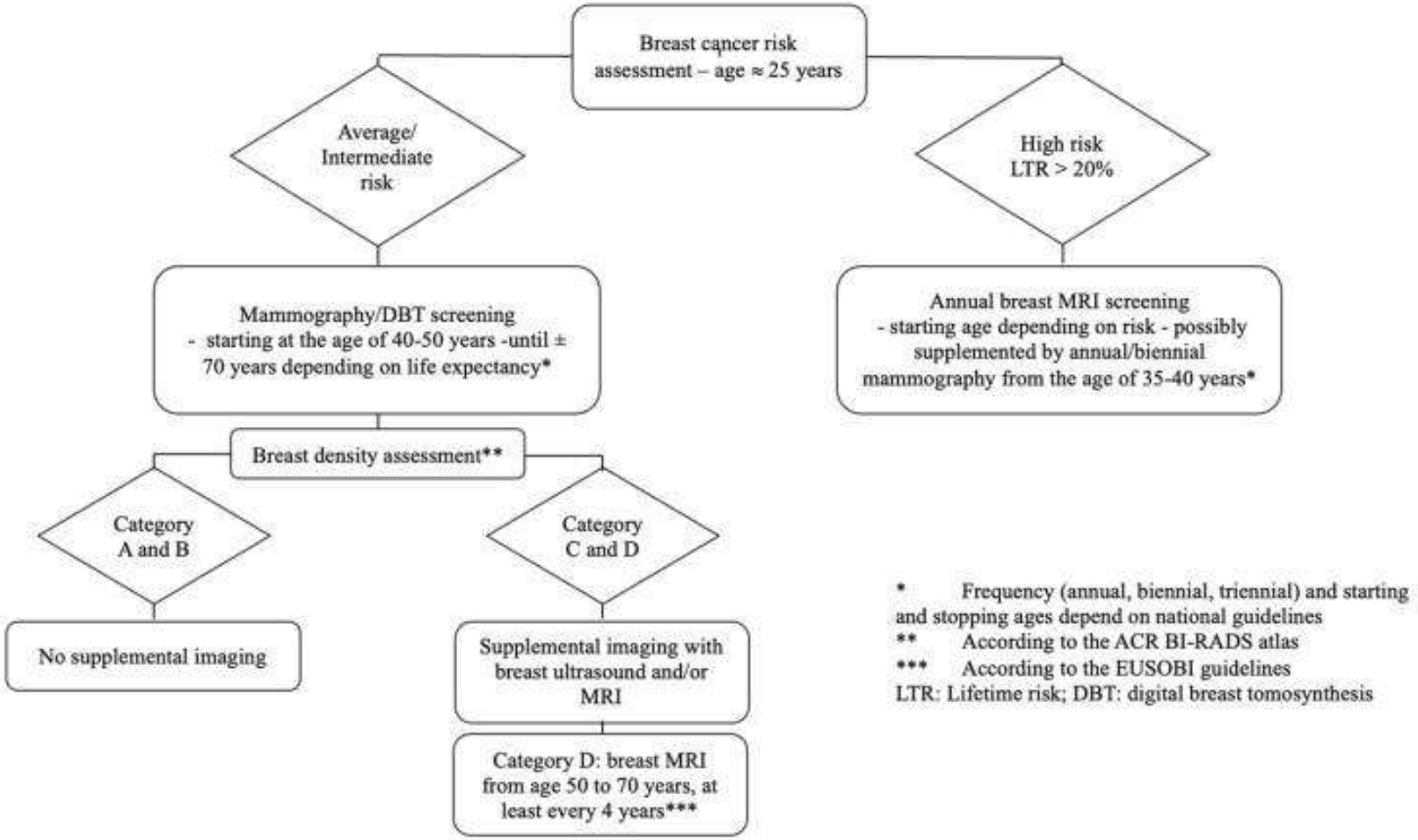
- Speak to your patients early on, 25 years as a start
- Calculate risk (risk prediction models)
- Deep learning models applied to mammographic images may improve risk prediction
- Establish an individualised protocol / Several trials to investigate implementation of different screening modalities and schedules based on personal risk estimation for women not known to be at high risk
    - MyPeBS (My Personal Breast Cancer Screening) Europe
    - WISDOM (Women Informed to Screen Depending On Measures of risk) United States
- Readjust if needed (becomes symptomatic, receives a biopsy, radiation for other reasons)



* Frequency (annual, biennial, triennial) and starting and stopping ages depend on national guidelines
** According to the ACR BI-RADS atlas
*** According to the EUSOBI guidelines
LTR: Lifetime risk; DBT: digital breast tomosynthesis

Marcon et al. Eur Radiol. 2024 Apr 24. doi: 10.1007/s00330-024-10740-5

Table 1 Summary recommendations on breast cancer screening

Recommendations on breast cancer screening
• Regular mammography should be considered the mainstay of breast cancer screening (evidence level I); digital breast tomosynthesis can be performed as an alternative.
• Women at high risk of breast cancer: screening should start as early as 25 years of age with annual breast MRI (evidence level I), supplemented with mammography from age 35 to 40 years.
• Women at intermediate risk of breast cancer: supplemental screening, including digital breast tomosynthesis, breast ultrasound, breast MRI, and possibly contrast-enhanced mammography may be beneficial. The most appropriate imaging modalities should be adjusted to patient characteristics.
• Women with extremely dense breast tissue: supplemental screening with MRI should be performed preferably every 2–3 years (evidence level I). If MRI is not available, supplemental ultrasound can be performed as an alternative although the evidence remains more limited.
• Whenever possible, risk assessment should be performed at a young age (≈25 years) to effectively tailor screening recommendations.

Marcon et al. Eur Radiol. 2024 Apr 24. doi: 10.1007/s00330-024-10740-5

ESMO DEEP DIVE: BREAST CANCER

THANK YOU SO MUCH FOR YOUR ATTENTION

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BREAKTHROUGHS IN PERSONALISED, MOLECULARLY-INFORMED RISK PREDICTION, SCREENING AND EARLY DETECTION OF BREAST CANCER

Lifestyle changes: IS PREVENTION POSSIBLE?

Suzette Delaloge

Head, Personalised Cancer Prevention Programme, Department of Cancer Medicine

Gustave Roussy, Villejuif, France

INTERCEPTION
GUSTAVE ROUSSY
Le programme de prévention personnalisée des cancers

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DISCLOSURES

Suzette Delaloge

Research support (to my institution)

AstraZeneca, MSD, BMS, Sanofi, Taiho, Novartis, European Commission, INCa, Banque des Territoires, Fondation Philanthropia

Honoraria for lectures and advisory boards (to my institution)

Astra Zeneca, Gilead, Novartis, Elsan, Besins, Sanofi, Exact Sciences, Lilly

Travel support

Novartis (national meeting)

LIFESTYLE CHANGES: IS PREVENTION POSSIBLE?

Towards stratified/personalized breast cancer prevention

- How does it work?
- Epidemiological data
- Interventional results
- How and for whom?
- Conclusions

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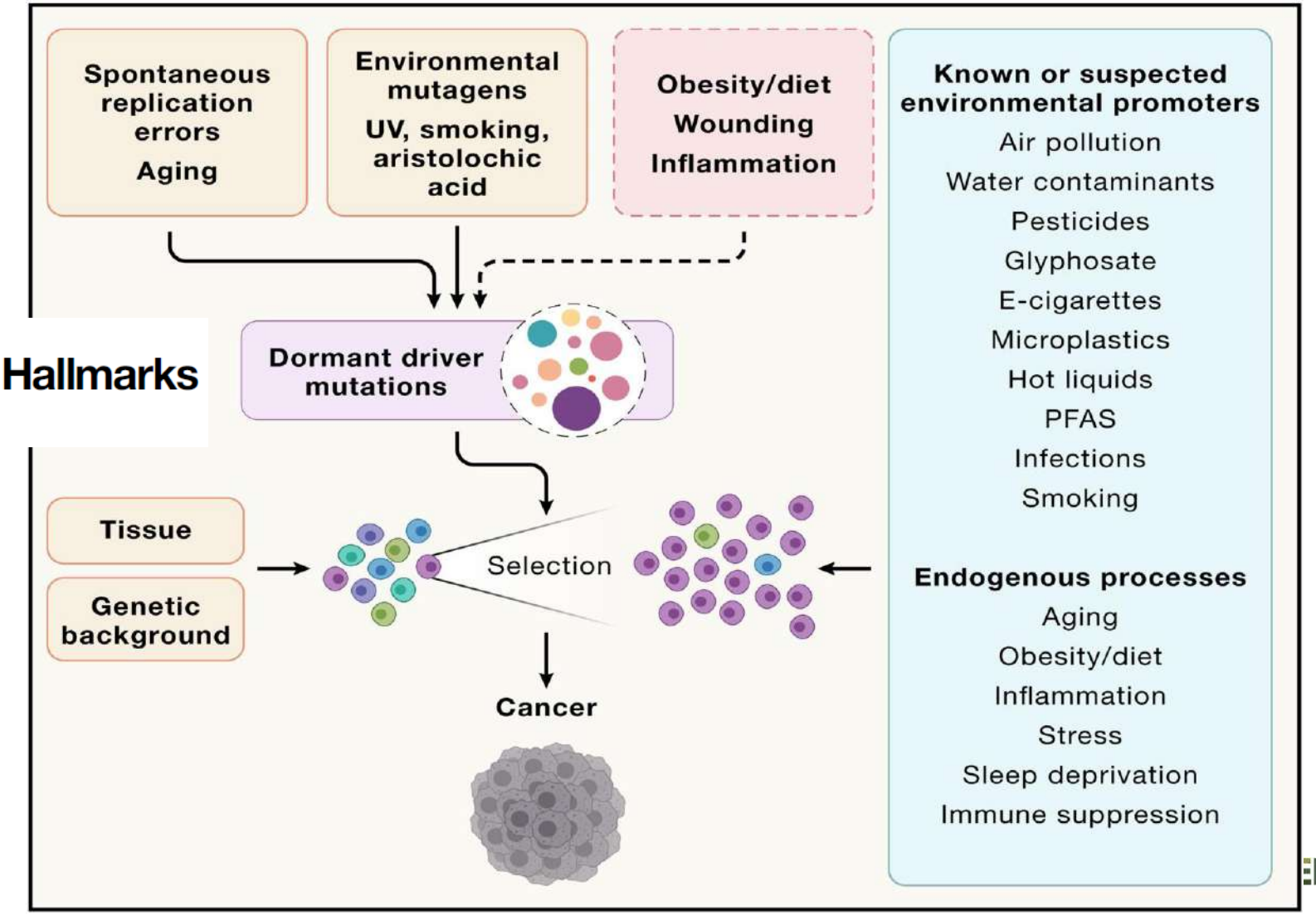
- Interventional results
- How and for whom?
- Conclusions

REAPPRAISING CARCINOGENESIS: ONE'S INSTANTANEOUS RISK OF CANCER IS DEPENDENT ON AGE, TIME, GENETIC BACKGROUND, EXPOSURES

Many new potential early detection and prevention targets are arising

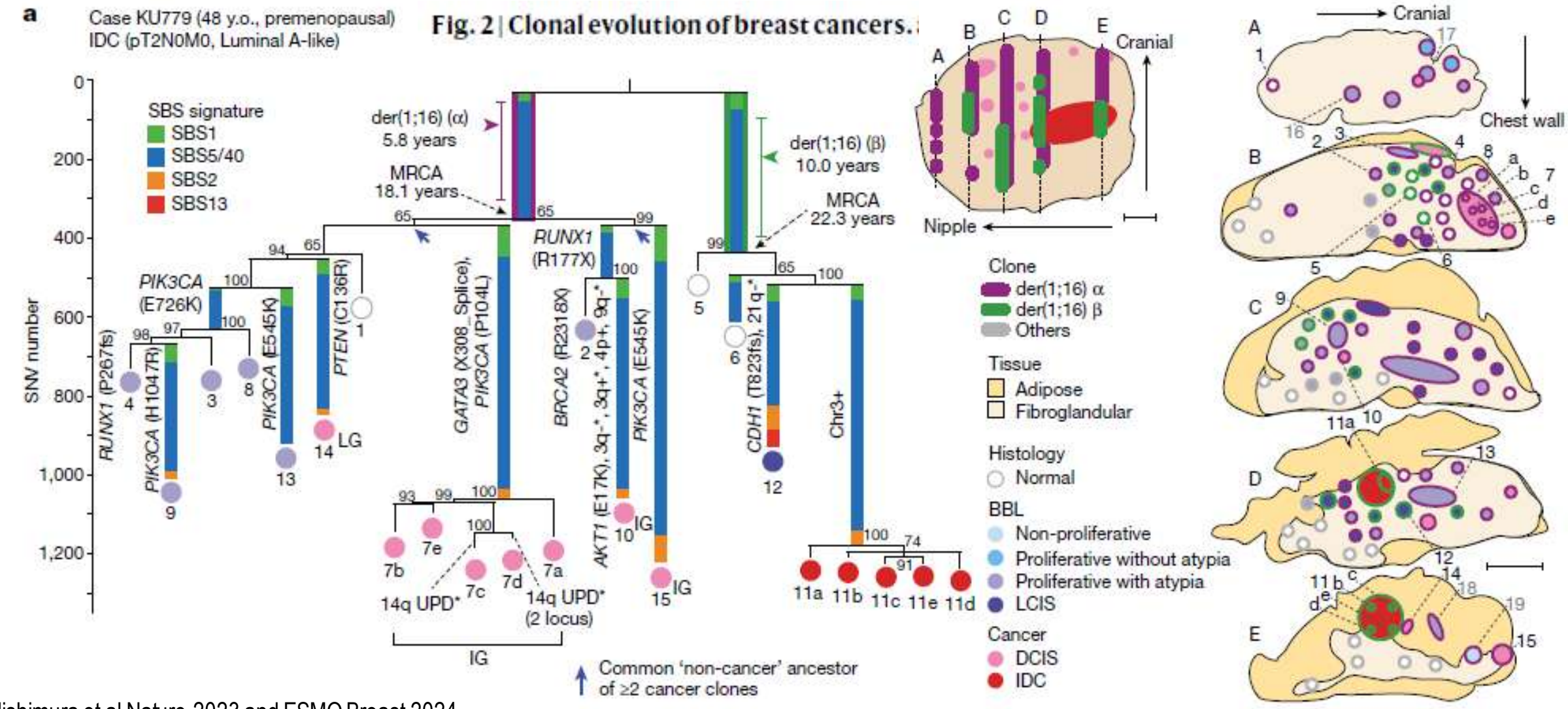
Perspective

Embracing cancer complexity: Hallmarks of systemic disease



Swanton et al *Cell* 2024 1871589-1616

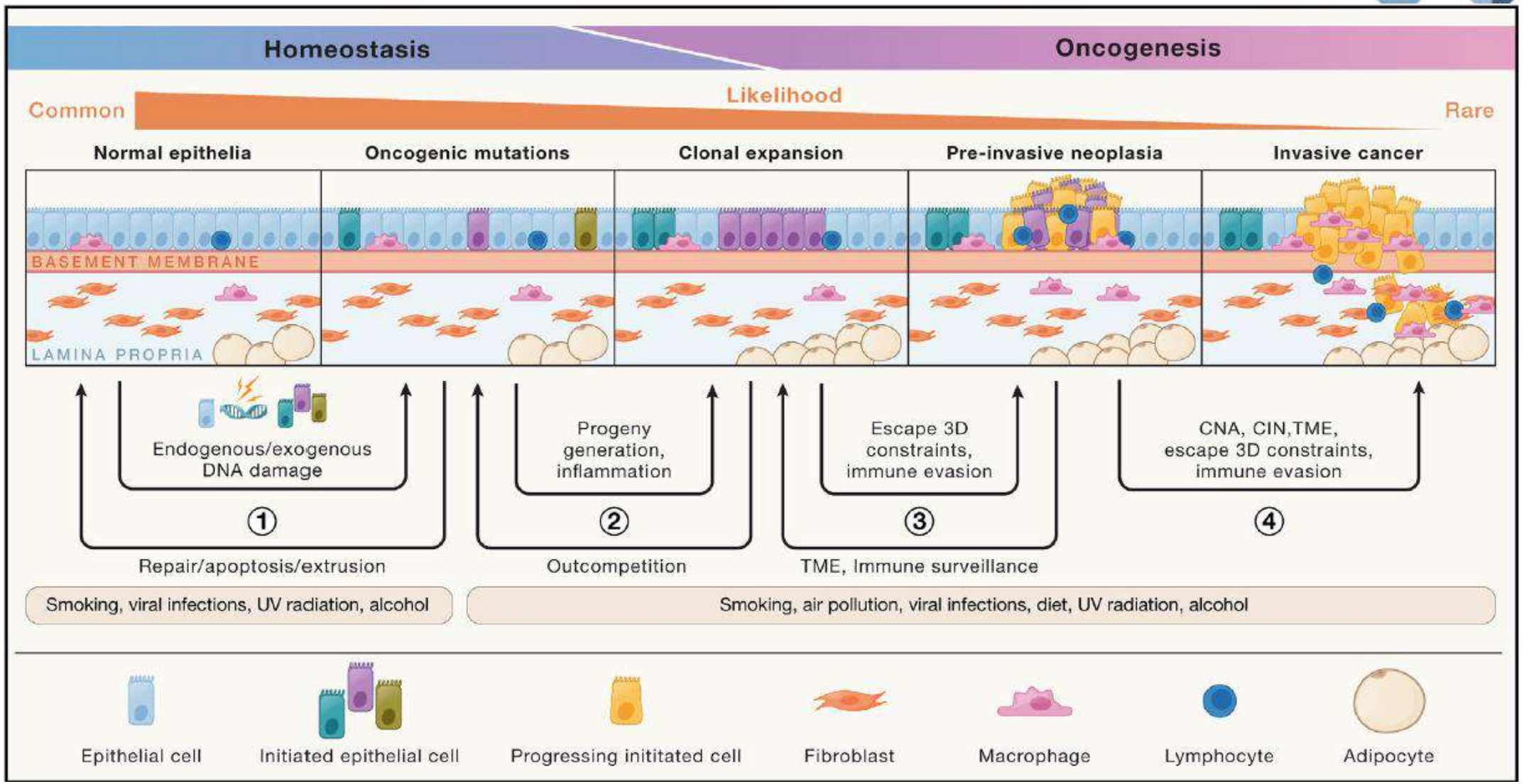
THE CLONAL EXPANSION OF HEALTHY MUTANT BREAST CELLS MAKES THE BED OF A (NON OBLIGATORY) TRANSFORMATION (AND IS EXPOSURE-SENSITIVE)



Nishimura et al Nature 2023 and ESMO Breast 2024

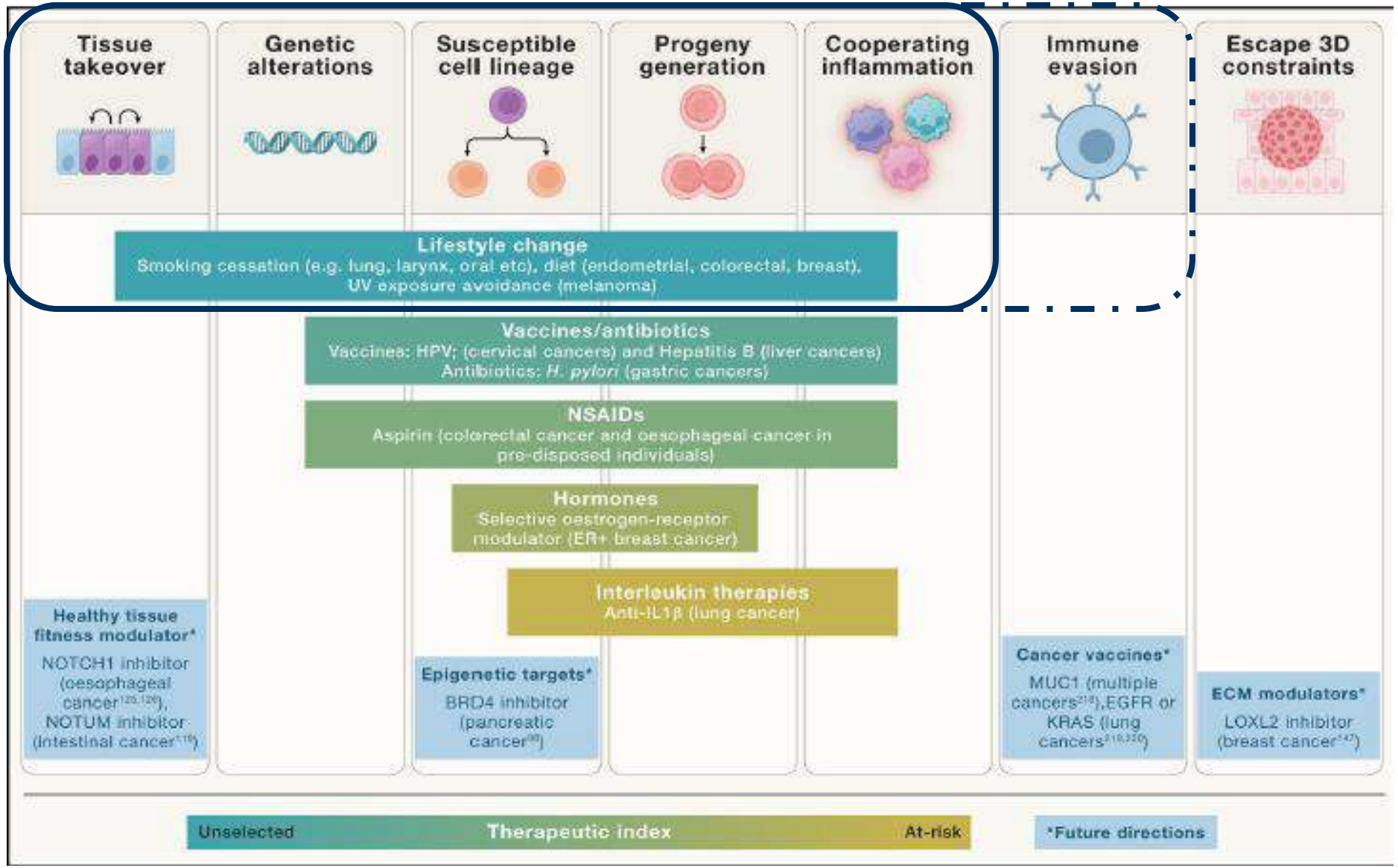
A REVISITED VISION OF CARCINOGENESIS

Weeden, Swanton, Impact of risk factors on early cancer evolution, Cell 2023



IMPACT ON PRIMARY PREVENTION INTERVENTIONS

Weeden, Swanton, Impact of risk factors on early cancer evolution, Cell 2023



HOW DOES IT WORK: PHYSICAL ACTIVITY

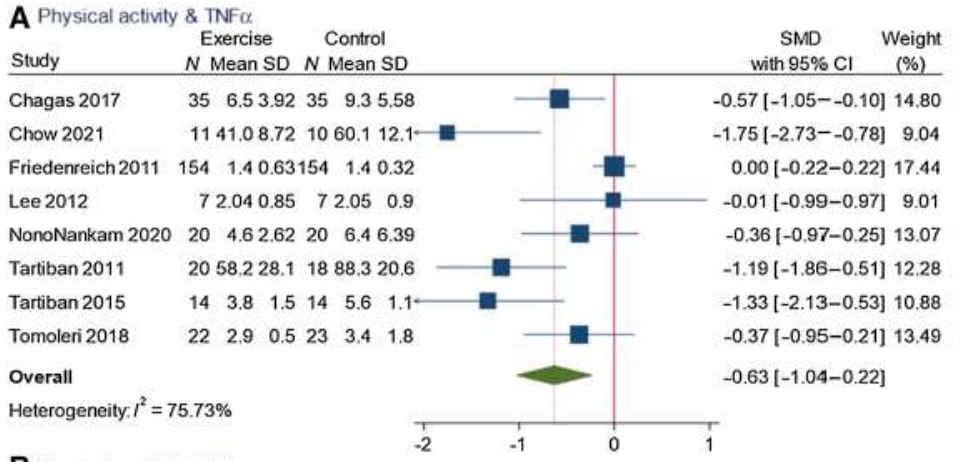
Physical activity → ? → Breast cancer risk

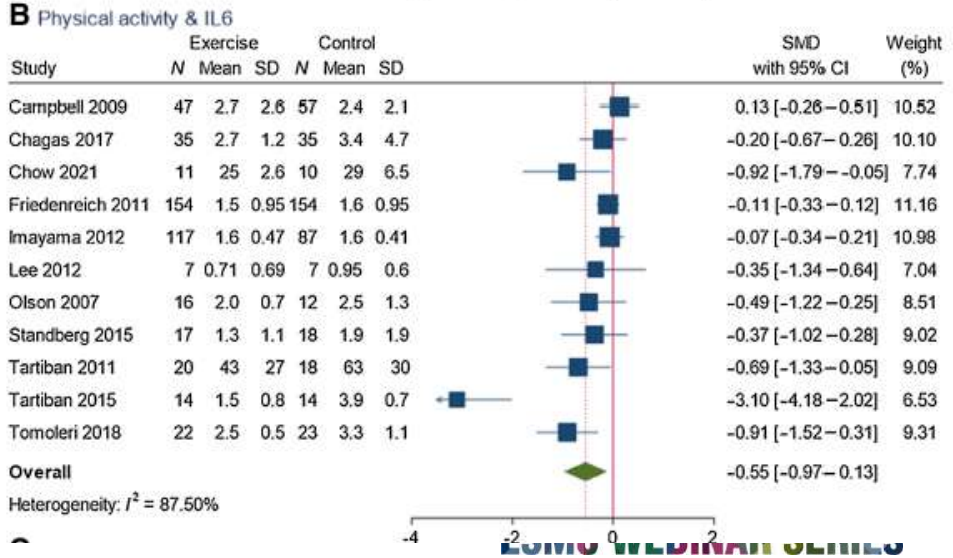
↓

Inflammation

Physical activity has a favorable effect on adiponectin, TNFa, IL6

Outcome	Meta-analysis study *n* (participant *n*)	Meta-analysis effect estimate SMD (95% CI)	GRADE judgment
CRP	12 (1, 210)	−0.27 (−0.62 to 0.08)	Low[a,b]
Cytokines			
TNFα	8 (564)	−0.63 (−1.04 to −0.22)	Moderate[a]
IL1B	NA	NA	Very low
IL6	11 (895)	−0.55 (−0.97 to −0.13)	Moderate[a]
IL8	NA	NA	Very low
IL10	NA	NA	Very low
Adipokines			
Adiponectin	5 (645)	0.01 (−0.14 to 0.17)	High
Leptin	4 (586)	−0.50 (−1.10 to 0.09)	Low[a,b]





Swain et al CEBP 2023

HOW DOES IT WORK: PHYSICAL ACTIVITY

Physical activity → ? → Breast cancer risk

↓

Metabolism

Physical activity has a favorable effect on the glucose metabolism

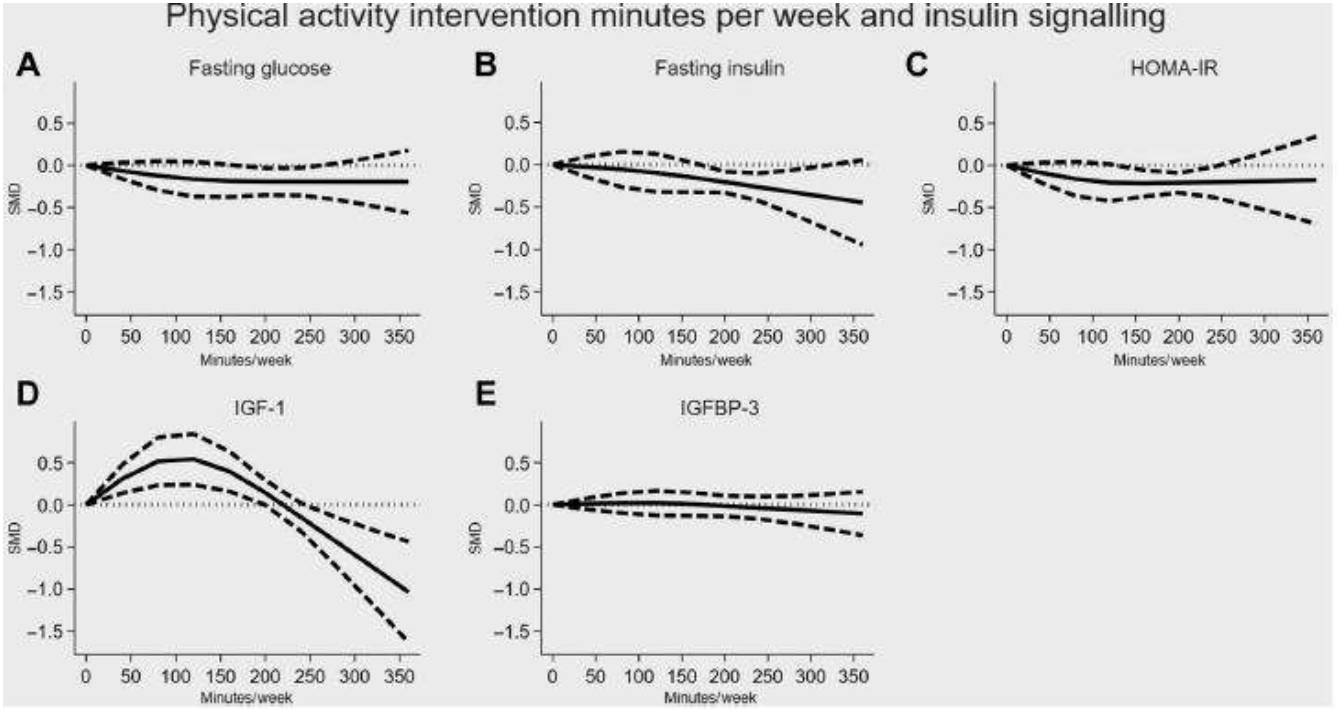


Table 1. GRADE appraisal for physical activity–insulin/IGF signaling pathways.

Outcome	Meta-analysis study *n* (participant *n*)	Meta-analysis effect estimate SMD (95% CI)	GRADE judgment
Fasting glucose	20 (1,454)	−0.17 −0.34 to −0.01)	Low[a]
Fasting insulin	18 (1,380)	−0.22–0.32 to −0.11)	High
HOMA-IR	11 (1,160)	−0.21–0.33 to −0.10)	High
C-Peptide	NA	NA	Very low[b]
HBA1c	NA	NA	Very low[b]
IGF-1	76 (1,316)	0.36 (0.05–0.67)	Low[c]
IGFBP-1	NA	NA	Very low[b]
IGFBP-3	6 (1,026)	0.03 (−0.16, 0.09)	High
IGF-1: IGFBP-3	5 (1,003)	−0.04 (−0.17, 0.08)	High

Drummond et al CEBP 2023

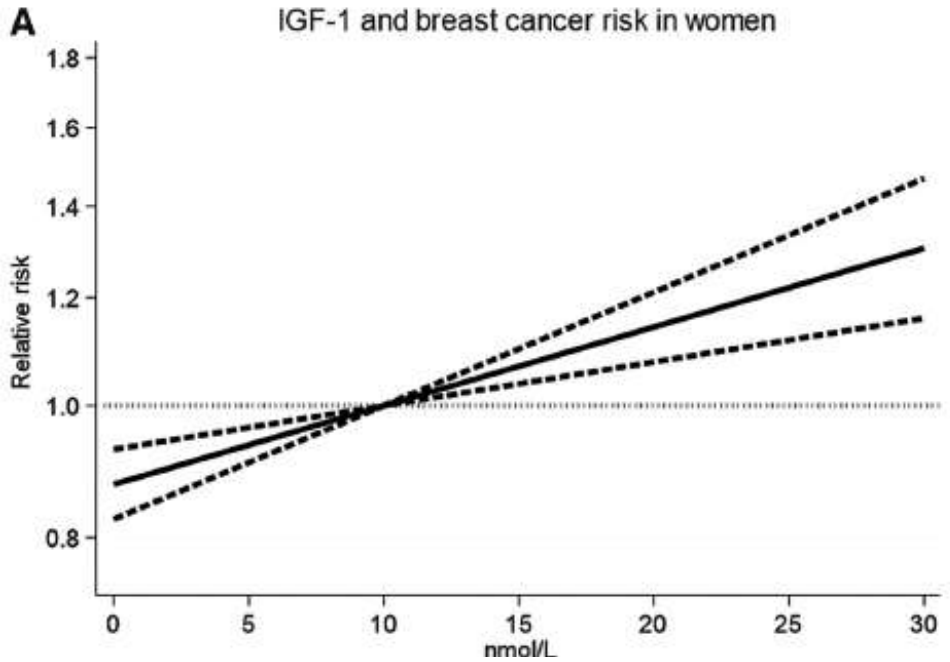
HOW DOES IT WORK: PHYSICAL ACTIVITY

Physical activity → ? → Breast cancer risk

↓

Metabolism

The glucose metabolism influences breast cancer risk



Outcome, menopausal status	Study type, number, participant numbers (*n*)	Effect estimates (RR, 95% CI)	Quality of evidence determination: ROB	Criteria for downgrading: Inconsistency	Imprecision	Pub bias	Criteria for upgrading	Quality of evidence final
Insulin								
All women	Observational[b], 3 (2,139)	1.12 [0.30–1.94]	Serious	No	Yes	?	None	**Very low**
All women	Mendelian randomization, 2 (193,415)	1.80 [0.18–8.06][63] 1.16 [0.96–1.41][62]	–	No	Yes	–		
IGF-1								
All women	Observational, 9 (215,500)	1.21 [1.10–1.31] *	Moderate	No	No	Yes	Dose–response	**Moderate**
IGFBP-3 adjusted	Observational, 3 (3,650)	0.97 [0.70–1.24]	–	–	No	–		
All women	Mendelian randomization, 1 (228,951)	1.05 [1.01–1.10][65]						
IGFBP3								
All women	Observational, 6 (6,692)	1.03 [0.81–1.24]	Moderate	No	No	No	None	**Moderate**
All women	Mendelian randomization, 1 (228,951)	1.00 [0.97–1.04][65]	–	–	No	–		
C-peptide								
All women	Observational, 4 (5,452)	1.16 [0.93–1.40]	Serious	No	No	?	None	**Very low**
Glucose[a]								
Premenopausal	Observational, 1 (334)	2.8 [1.2–6.5][56]*	Serious	Yes	Yes	–	None	**Very low**
Postmenopausal		1.63 [0.59–4.46][56]	–	No	Yes	–		
Postmenopausal	Observational, 1 (5,450)	1.14 [0.60–2.16][55]	–	–	Yes	–		
All women	Mendelian randomization, 2 (411,257)	1.03 [0.85–1.25][64]						
All women		1.06 [0.95–1.17][62]						
Post- menopausal		0.63 [0.50–0.79][63]						
All women: 2hr glucose	Mendelian randomization, 1 (11,109)	1.50 [1.21–1.86][62]*						
HbA1c								
Premenopausal	Observational, 1 (7,442)	1.08 [0.65–1.79][57]	Moderate	No	Yes	–	None	**Very low**
Postmenopausal	Observational, 1 (27,110)	0.73 [0.54–0.98][45]	–	–	Yes	–		
All women	Mendelian randomization, 1 (228,951)	1.02 [0.73–1.45][64]						

Drummond et al CEBP 2023

HOW DOES IT WORK: PHYSICAL ACTIVITY

Physical activity → ? → Breast cancer risk

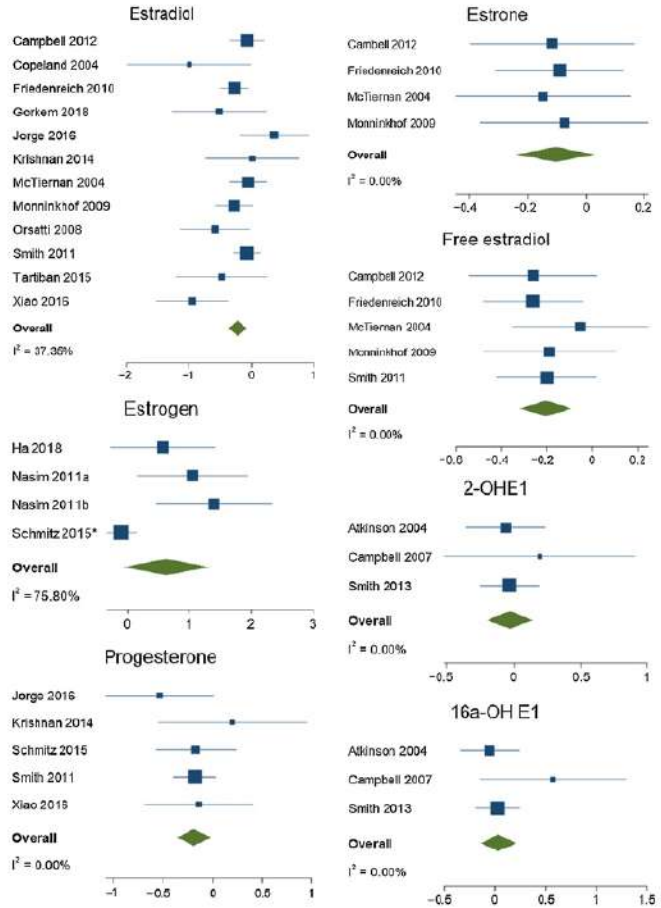
↓

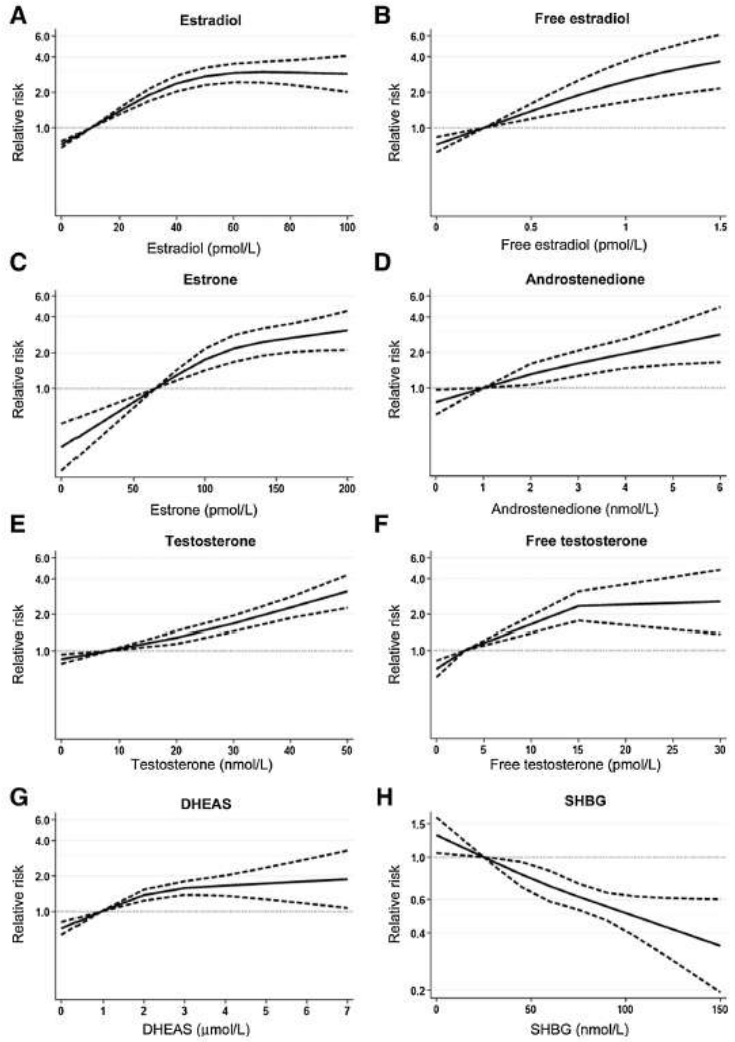
Hormones

Physical activity regulates hormone levels

↓

Hormone levels are associated with breast cancer risk





Swain et al CEBP 2022 & CEBP 2022

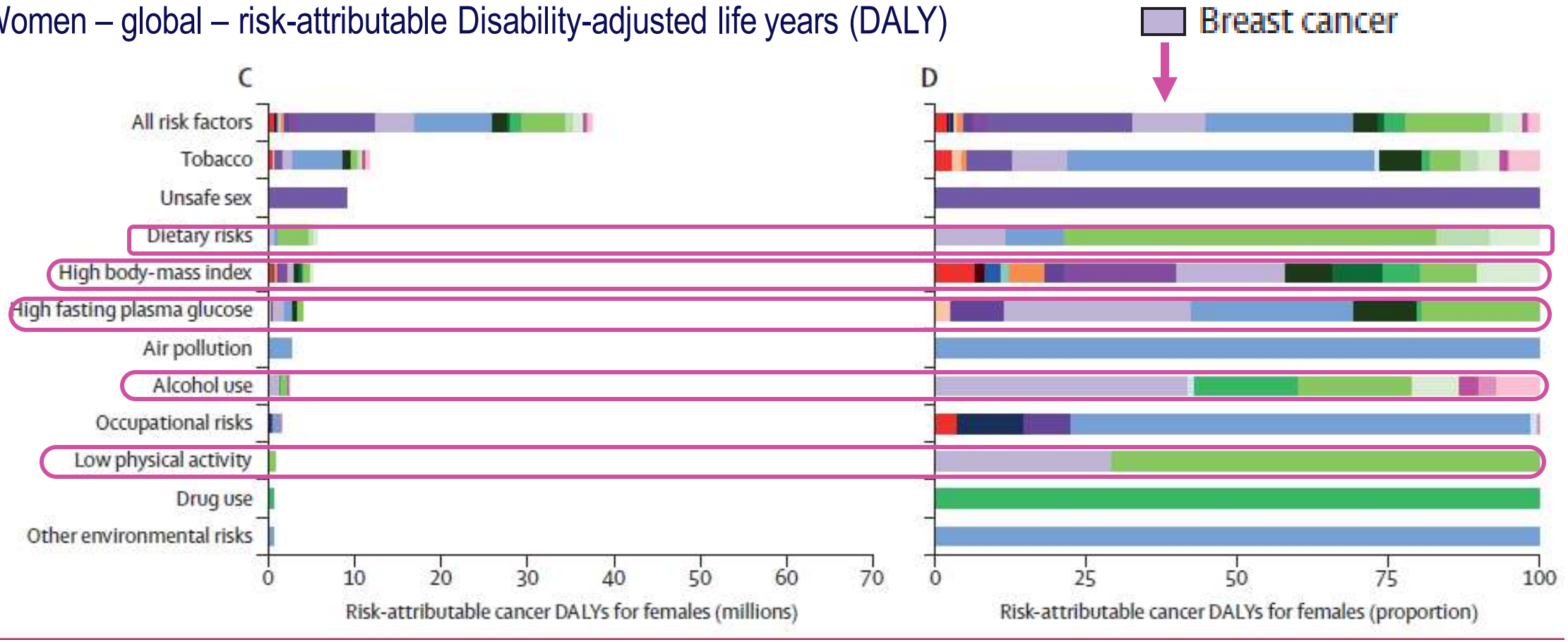
LIFESTYLE CHANGES: IS PREVENTION POSSIBLE?

Towards stratified/personalized breast cancer prevention

- How does it work?
- Epidemiological data
- Interventional results
- How and for whom?
- Conclusions

RISK-ATTRIBUTABLE CANCERS

Women – global – risk-attributable Disability-adjusted life years (DALY)



Global burden of disease, Lancet 2022

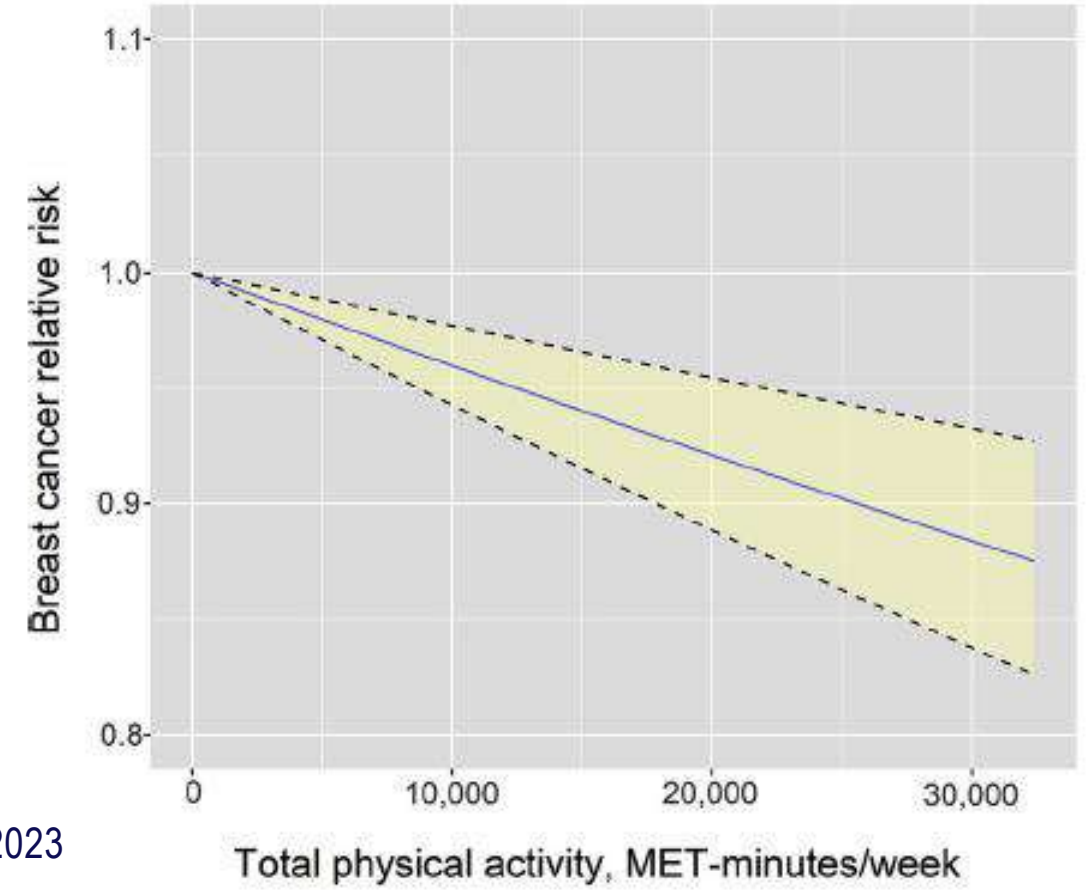
BC INCIDENCE: WHAT IS THE MAGNITUDE OF THE EFFECTS IN THE GENERAL POPULATION?

Risk factor	Categories	RR (95% confidence interval)
Hormonal and reproductive factors		
Age at menarche (years)	11	1.0 (reference)
	15	0.69 (0.65–0.74)
Parity	Nulliparous	1.0 (reference)
	Parous	1.26 (1.10–1.44)
Age at first full-term pregnancy (years)	20	0.73 (0.63–0.86)
	30	1.16 (0.96–1.41)
Breastfeeding	Per 12 months of total breastfeeding	0.96 (0.94–0.97)
Age at menopause (years)	45	1.0 (reference)
	55	1.44 (1.26–1.64)
Type of menopause	Natural	1.0 (reference)
	Bilateral oophorectomy	0.89 (0.80–0.98)
Postmenopausal hormone use	None	1.0 (reference)
	Estrogen only[a]	1.18 (1.08–1.30)
	Combined estrogen–progestogen[a] for > 5 years	1.63 (1.22–2.18)
Lifestyle factors		
Alcohol consumption	Per 12 g/day	1.12 (1.09–1.14)
	Premenopausal	1.09 (1.01–1.17)
	Postmenopausal	1.08 (1.05–1.10)
Tobacco smoking (pack-years)	≥ 20	1.28 (1.17–1.39)
Weight increase (per 5 kg/m² increase in BMI)	Postmenopausal	1.12 (1.08–1.16)
	Premenopausal	0.92 (0.88–0.97)
Physical activity, high vs low (METs)	Premenopausal	0.87 (0.84–0.92)
	Postmenopausal	0.77 (0.72–0.84)
	Moderate physical activity (3–5.9 METs)	0.81 (0.72–0.92)
Non-modifiable factors		
Height (per 5 cm increase)	Premenopausal	1.09 (1.05–1.14)
	Postmenopausal	1.11 (1.09–1.13)
	Any age	1.03 (1.01–1.04)
Age (years)	< 50	1.0 (reference)
	50–59	6.6 (6.5–6.7)
	60–69	9.2 (9.1–9.3)
	70–79	11.1 (10.9–11.2)
	≥ 80	10.1 (10.0–10.3)
Benign breast disease	No	1.0 (reference)
	Common epithelial hyperplasia	1.5–2.0
	Atypical epithelial hyperplasia	2.5–4.0
Breast density	Dense area, mean: 59.92–201.49 cm²	1.57 (1.18–1.67)
Ionizing radiation		
Radiation exposure		
Family and personal history of breast cancer		
Mother's age (years) at breast cancer	< 50	2.69 (2.29–3.15)
	≥ 50	1.88 (1.73–2.03)

IARC Handbook 2014

PHYSICAL ACTIVITY AND BREAST CANCER RISK: A LINEAR RELATIONSHIP

Light Intensity Activities	METs
Sleeping	0.95
Watching television	1.0
Writing, desk work, typing	1.3
Walking, household	2.0
Walking, 2.0 mph (3.2 km/h)	2.8
Moderate Intensity Activities	**METs**
Walking the dog	3.0
Walking, 2.8 - 3.2 mph (4.5 - 5.1 km/h), level, moderate pace	3.5
Calisthenics, (e.g., push ups, sit ups, pull-ups, lunges), moderate effort	3.8
Yard work, general, moderate effort	4.0
Mowing lawn, general	5.5
Bicycling, leisure, 9.4 mph (15.1 km/h)	5.8
Swimming laps, freestyle, light or moderate effort	5.8
Vigorous Intensity Activities	**METs**
Jogging, general	7.0
Snow shoveling, by hand, vigorous effort	7.5
Running, 5 mph (8.0 km/h)	8.3
Stair-treadmill ergometer, general	9.0
Swimming laps, freestyle, fast, vigorous effort	9.8
Running, 8 mph (12.9 km/h)	11.8



Diao et al Cancer Comm 2023

NUTRITION AND BREAST CANCER RISK: HOW BEST TO ASSESS ONE'S NUTRITIONAL PROFILE?

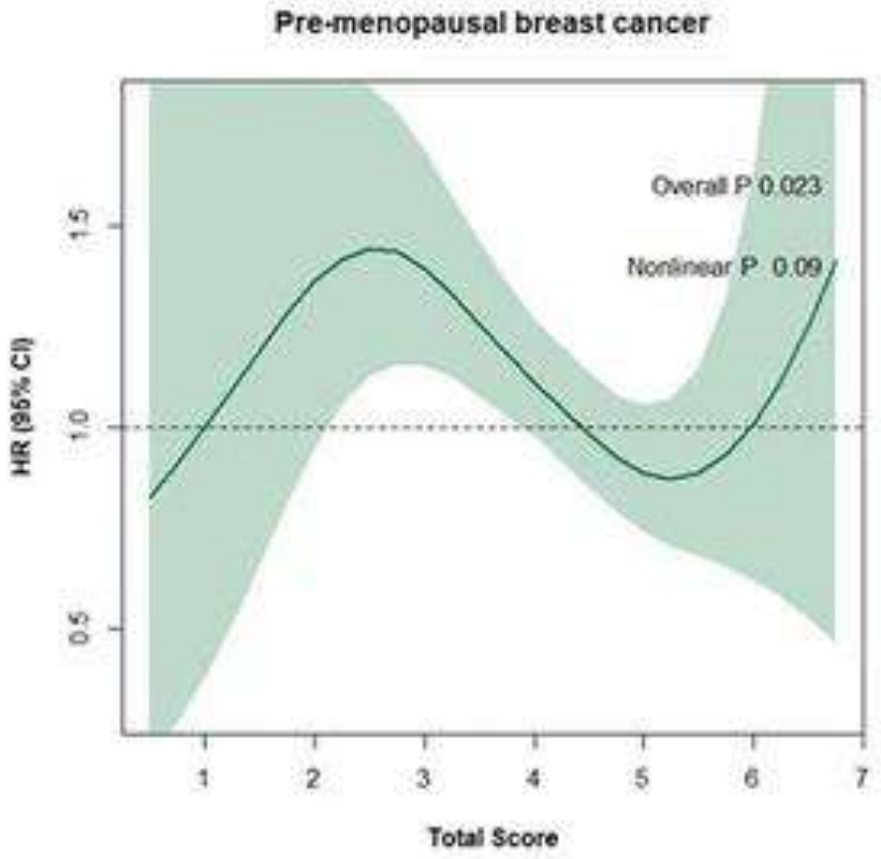
Adherence to the WCRF prevention recommendations has the highest level of evidence

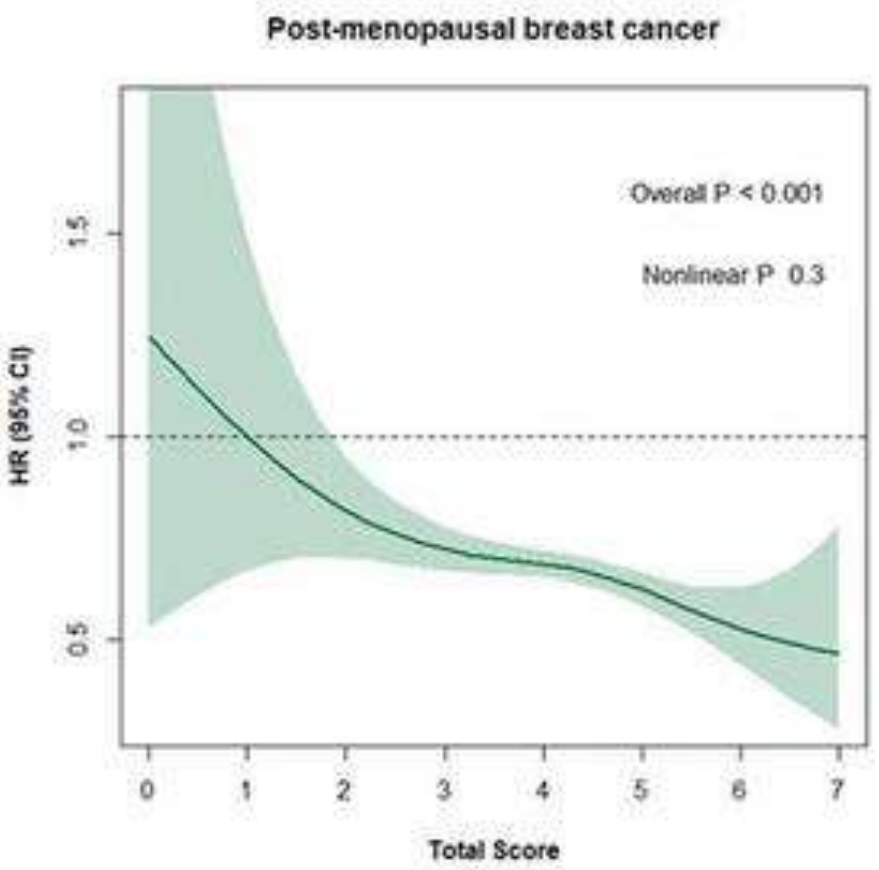
Shams-White Nutrients 2019

	2018 WCRF/AICR Recommendations	Operationalization of Recommendations	Points
1.	Be a healthy weight	**BMI (kg/m²):** [2]	
		18.5–24.9	0.5
		25–29.9	0.25
		<18.5 or ≥30	0
		Waist circumference (cm (in)): [2,3]	
		Men: <94 (<37) Women: <80 (<31.5)	0.5
		Men: 94–<102 (37–<40) Women: 80–<88 (31.5–<35)	0.25
		Men: ≥102 (≥40) Women: ≥88 (≥35)	0
2.	Be physically active	**Total moderate-vigorous physical activity (min/wk):** [4]	
		≥150	1
		75–<150	0.5
		<75	0
3.	Eat a diet rich in wholegrains, vegetables, fruit and beans	**Fruits and vegetables (g/day):** [5]	
		≥400	0.5
		200–<400	0.25
		<200	0
		Total fiber (g/day): [5]	
		≥30	0.5
		15–<30	0.25
		<15	0
4.	Limit consumption of "fast foods" and other processed foods high in fat, starches or sugars	**Percent of total kcal from ultra-processed foods (aUPFs):** [6]	
		Tertile 1	1
		Tertile 2	0.5
		Tertile 3	0
5.	Limit consumption of red and processed meat	**Total red meat (g/wk) and processed meat (g/wk):**	
		Red meat <500 and processed meat <21	1
		Red meat <500 and processed meat 21–<100	0.5
		Red meat >500 or processed meat ≥100	0
6.	Limit consumption of sugar-sweetened drinks	**Total sugar-sweetened drinks (g/day):**	
		0	1
		>0–≤250	0.5
		>250	0
7.	Limit alcohol consumption	**Total ethanol (g/day):**	
		0	1
		>0–≤28 (2 drinks) males and ≤14 (1 drink) females	0.5
		>28 (2 drinks) males and >14 (1 drink) females	0
8.	(Optional) For mothers: breastfeed your baby, if you can	**Exclusively breastfed over lifetime for a total of:**	
		6+ months	1
		>0–<6 months	0.5
		Never	0
		Total Score Range	0–7 (or 0–8)

EFFECT OF ADHERENCE TO RECOMMENDATIONS ON BREAST CANCER RISK

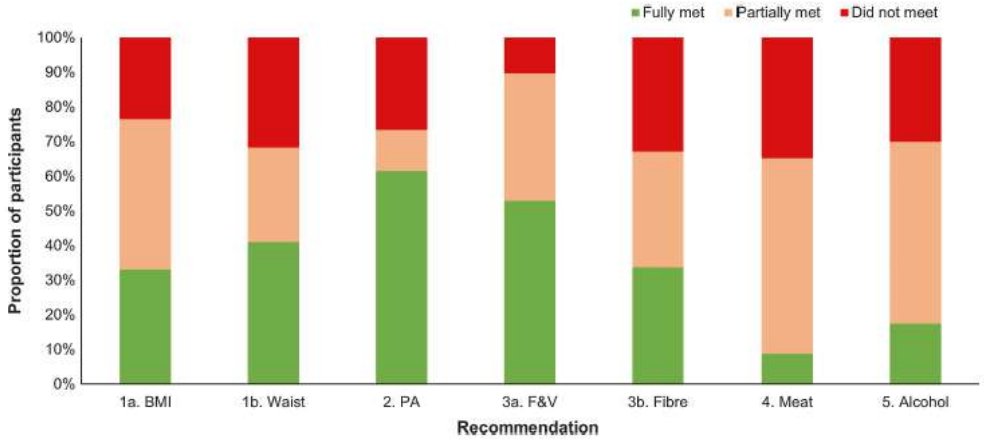
Adherence to the WCRF prevention recommendations and breast cancer risk in the UK Biobank





Macolmson BMC Med 2023

EFFECT OF ADHERENCE TO RECOMMENDATIONS ON BREAST CANCER RISK



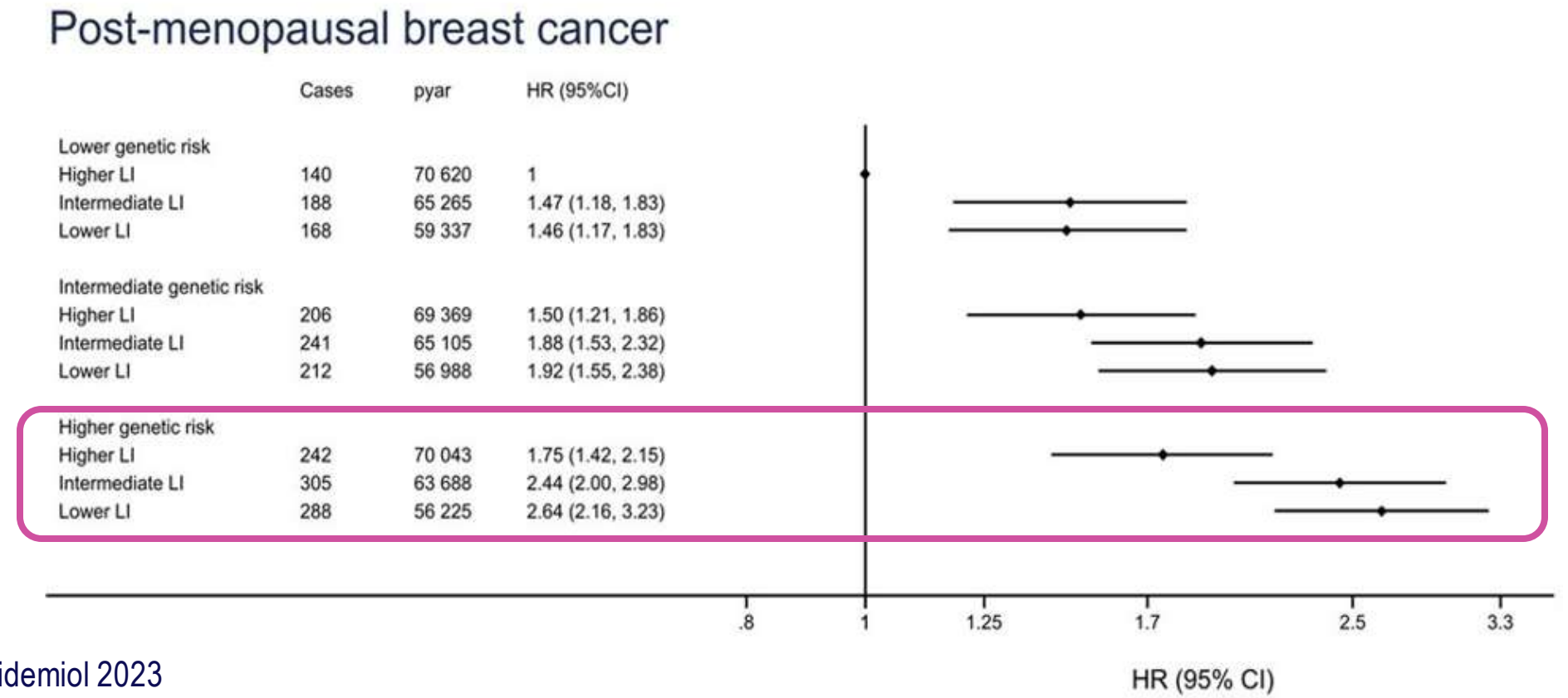
Adherence to the WCRF prevention recommendations (abbreviated score, 5 points) and breast cancer risk in the UK Biobank: effect on cancer risk by 1 point increment

Cancer site	Total	Incident cancers	Model 1 HR (95% CI)	Model 1 P	Model 2 HR (95% CI)	Model 2 P
All cancers combined	284,553	23,448	**0.92 (0.91–0.93)**	**<0.001**	**0.93 (0.92–0.95)**	**<0.001**
Prostate	139,240	5,677	**1.03 (1.00–1.06)**	**0.046**	1.02 (0.99–1.05)	0.192
Breast	147,655	4,014	**0.90 (0.87–0.93)**	**<0.001**	**0.90 (0.87–0.94)**	**<0.001**
Premenopausal	2,705	359	0.93 (0.82–1.04)	0.183	0.91 (0.81–1.02)	0.123
Postmenopausal	144,950	3,655	**0.89 (0.86–0.93)**	**<0.001**	**0.90 (0.86–0.93)**	**<0.001**
Colorectal	288,191	2,689	**0.86 (0.82–0.90)**	**<0.001**	**0.86 (0.83–0.90)**	**<0.001**
Colon	288,361	1,812	**0.84 (0.80–0.89)**	**<0.001**	**0.85 (0.80–0.89)**	**<0.001**
Distal	288,537	756	**0.84 (0.77–0.91)**	**<0.001**	**0.84 (0.77–0.91)**	**<0.001**
Proximal	288,554	965	**0.85 (0.79–0.91)**	**<0.001**	**0.86 (0.80–0.92)**	**<0.001**
Rectum	288,518	1,052	**0.86 (0.80–0.92)**	**<0.001**	**0.87 (0.81–0.93)**	**<0.001**
Lung	288,493	1,805	**0.79 (0.75–0.83)**	**<0.001**	**0.89 (0.84–0.94)**	**<0.001**
Kidney	288,593	764	**0.81 (0.75–0.88)**	**<0.001**	**0.83 (0.76–0.90)**	**<0.001**
Pancreas	288,629	745	**0.85 (0.79–0.92)**	**<0.001**	**0.86 (0.79–0.94)**	**<0.001**
Uterus	148,395	684	**0.81 (0.74–0.88)**	**<0.001**	**0.79 (0.73–0.86)**	**<0.001**
Esophagus	288,627	555	**0.78 (0.71–0.86)**	**<0.001**	**0.82 (0.75–0.90)**	**<0.001**
Ovary	148,434	482	1.00 (0.90–1.11)	0.983	1.00 (0.90–1.11)	0.940
Bladder	288,603	549	**0.88 (0.80–0.97)**	**0.001**	0.93 (0.84–1.02)	0.118
Head and neck	288,626	445	0.96 (0.87–1.07)	0.464	1.01 (0.91–1.12)	0.888
Stomach	288,645	389	**0.86 (0.77–0.97)**	**0.011**	**0.89 (0.79–0.99)**	**0.038**
Liver	288,653	356	**0.79 (0.70–0.89)**	**<0.001**	**0.80 (0.72–0.90)**	**<0.001**
Gallbladder	288,687	153	0.94 (0.78–1.12)	0.483	0.94 (0.78–1.12)	0.483

Macolmson CEBP 2024

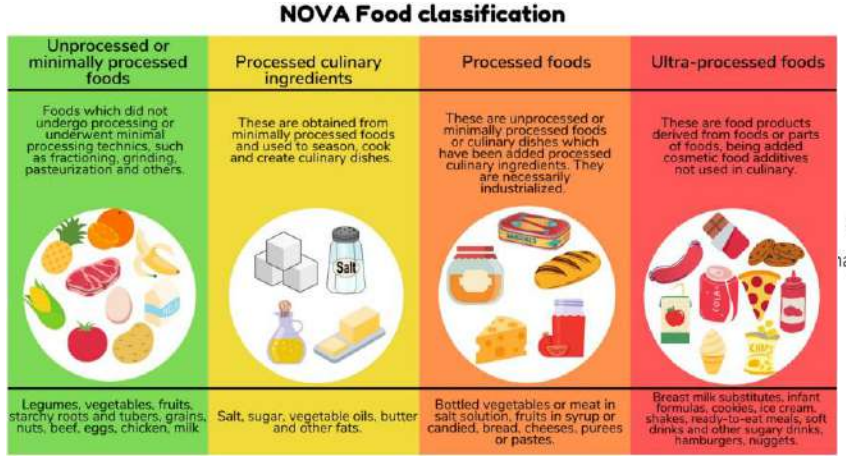
LIFESTYLE INDEX (LI) AND RISK OF BREAST CANCER: EVIDENCE WHATEVER THE RISK LEVEL

Prospective cohort, by PRS-defined risk level



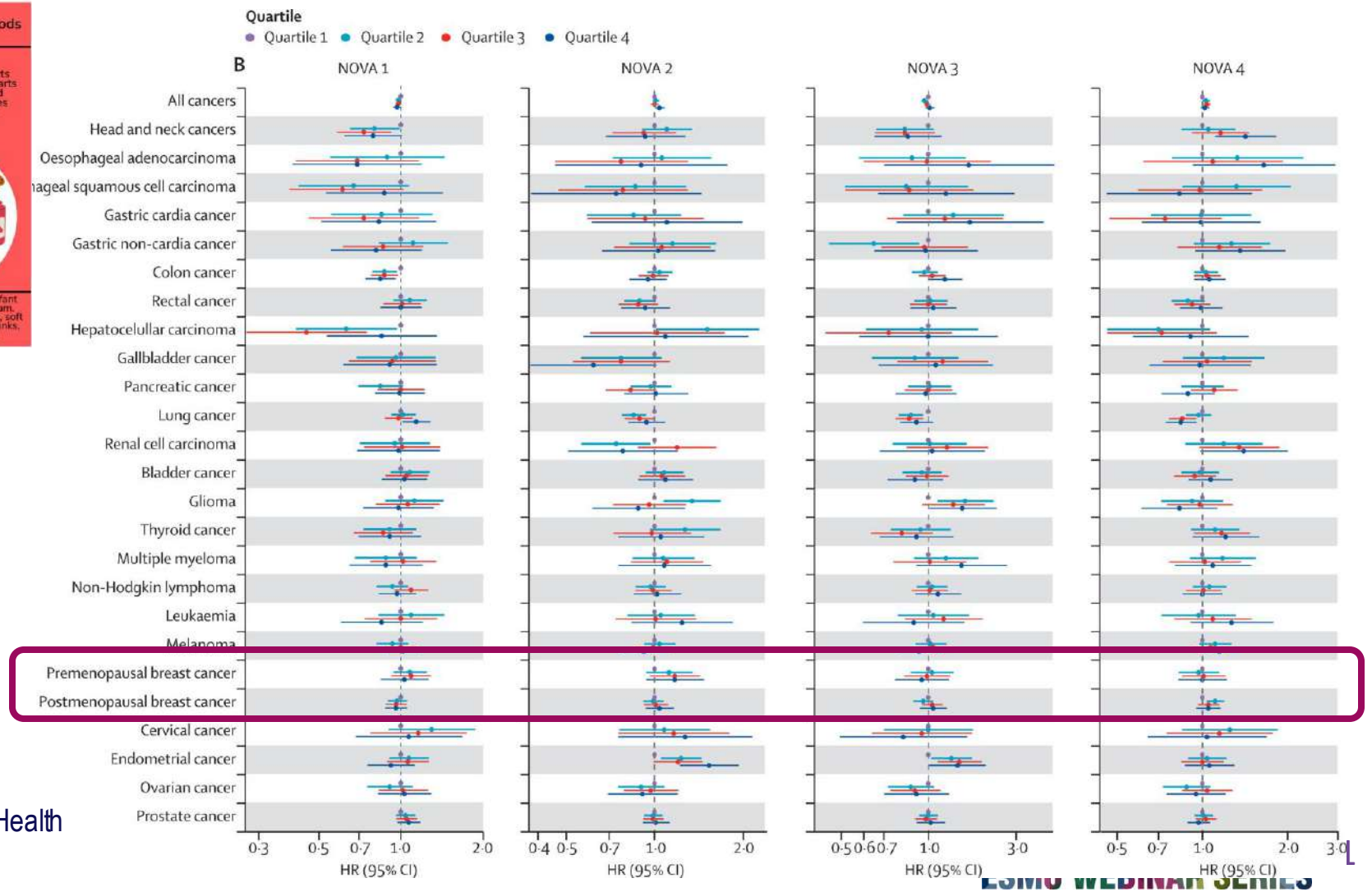
Byrne et al Int J Epidemiol 2023

NUTRITION: EMERGING TARGETS ULTRA PROCESSED FOOD CONSUMPTION



De Oliveira Front Nutr 2022

Postmenopausal breast cancer NOVA1 vs 4
Multiadjusted
HR 0·93, 0·90–0·97



Kliemann 2023 Lancet Planet Health

NUTRITION: EMERGING TARGETS

Many others emerging but limited evidence so far:

- Emulsifiers Sellem 2024 (HR = 1.24; 95% CI [1.03, 1.51]
- Western diet Castello 2024 (HR (95 % CI) 1.30 (0.98;1.72)
- Artificial sweeteners Debras 2023 HR = 1.22 [95% CI 1.01 to 1.48]
- Sugar drinks Chazelas 2019 1.22, 1.07 to 1.39
- Organic food....

LIFESTYLE CHANGES: IS PREVENTION POSSIBLE?

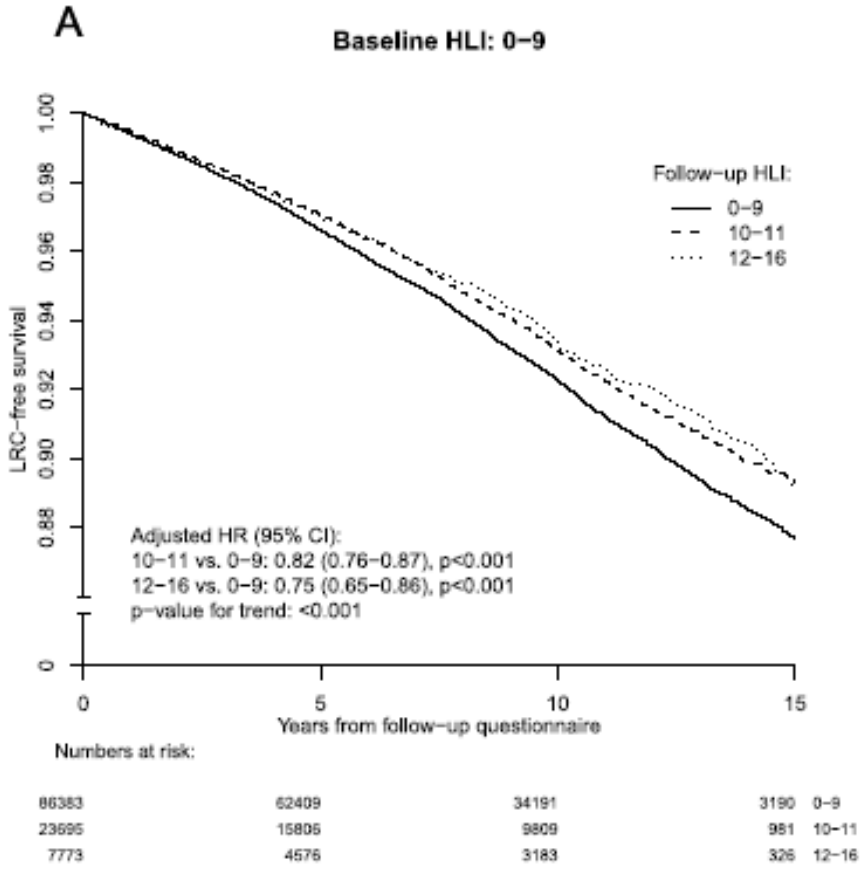
Towards stratified/personalized breast cancer prevention

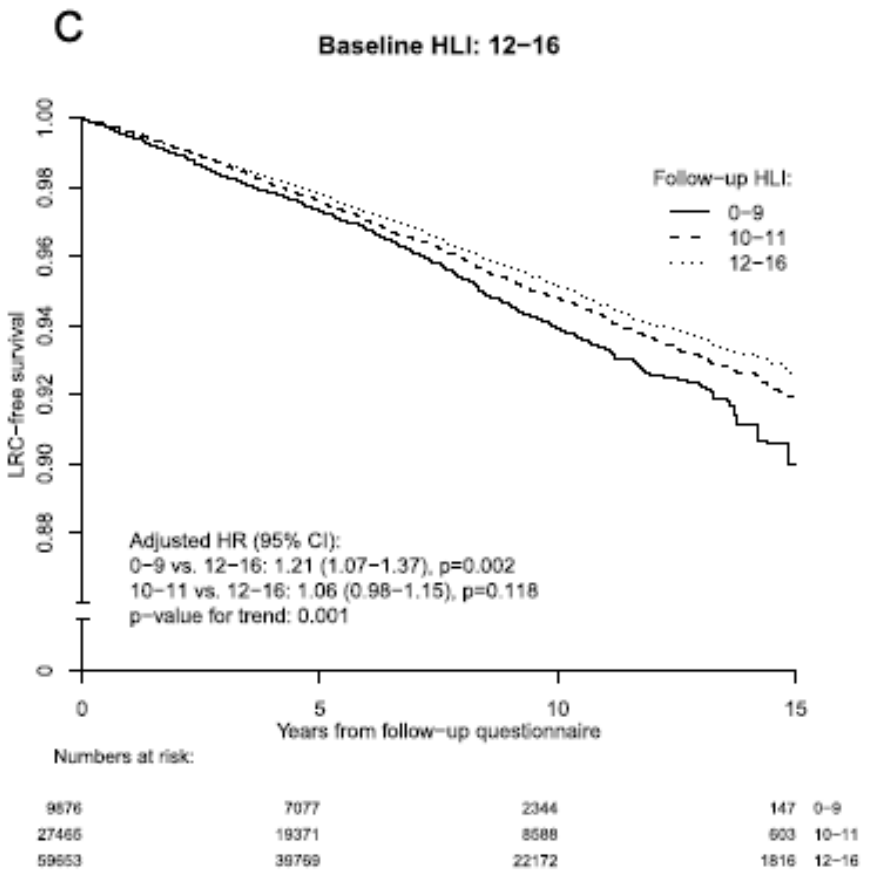
- How does it work?
- Epidemiological data
- Interventional results
- How and for whom?
- Conclusions

LIFESTYLE CHANGES AT MIDDLE AGE AND SUBSEQUENT RISK OF ANY CANCER

Decreased risk whatever the initial lifestyle index

EPIC cohort





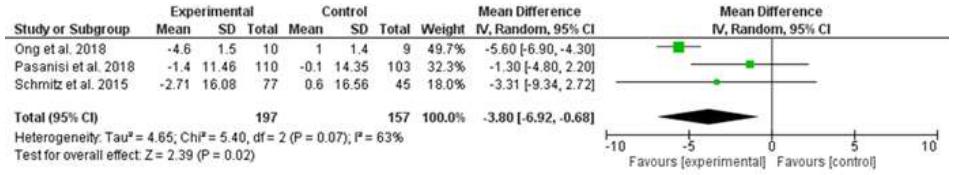
Botteri et al Eur J Epidemiol 2024

PRIMARY PREVENTION INTERVENTIONS ON EXPOSURE/LIFESTYLE FACTORS

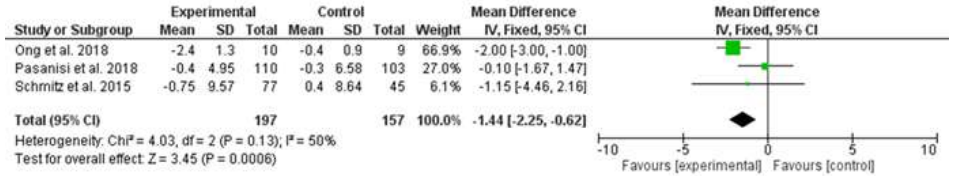
Plenty of epidemiological data, very little prospective intervention data

Studies primarily on surrogates

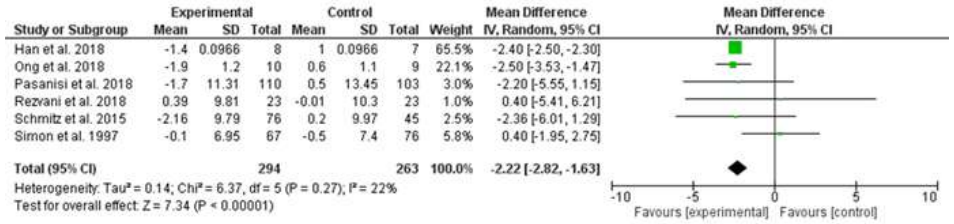
Fat mass



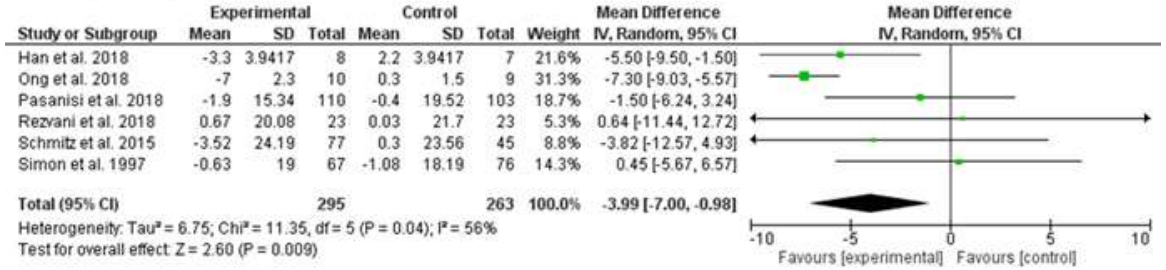
Lean mass



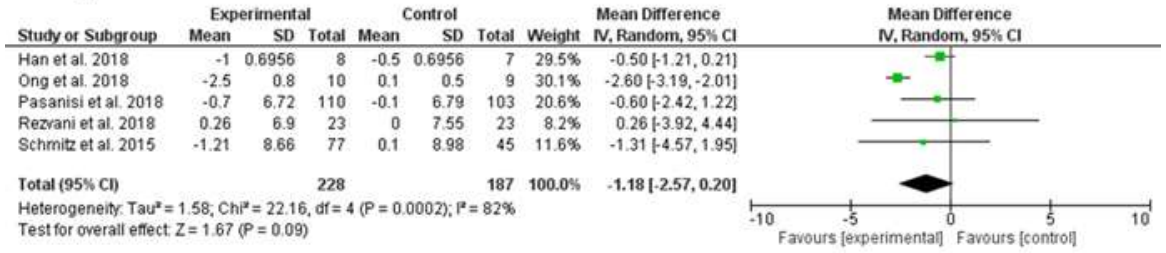
Body fat percentage



Body weight



Body mass index



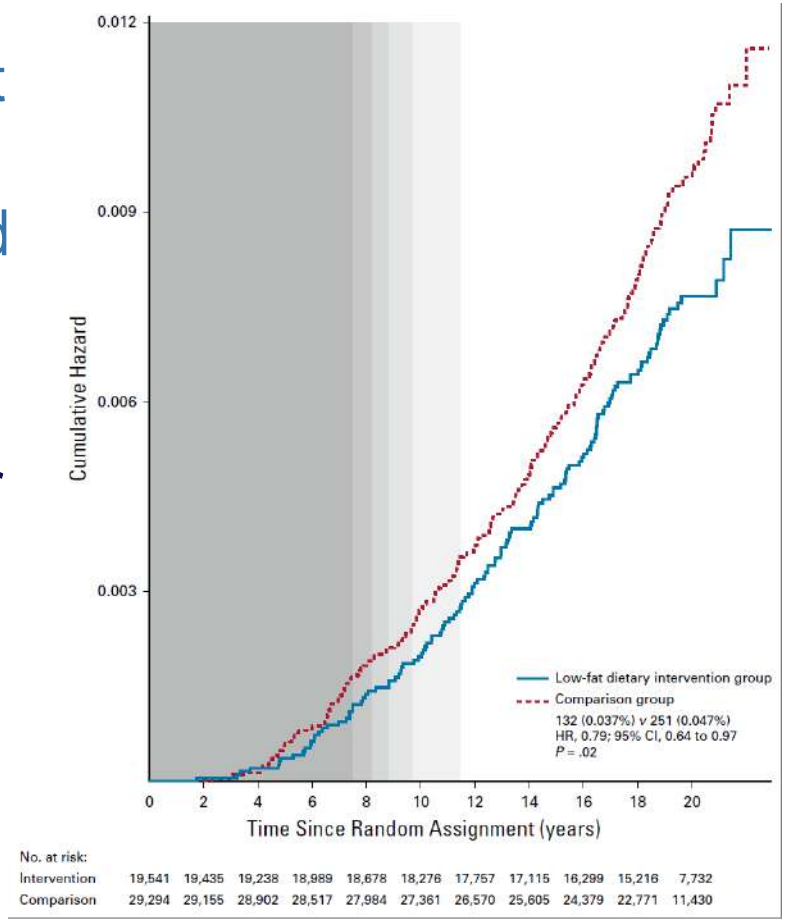
INTERVENTIONS ON EXPOSURE/LIFESTYLE FACTORS

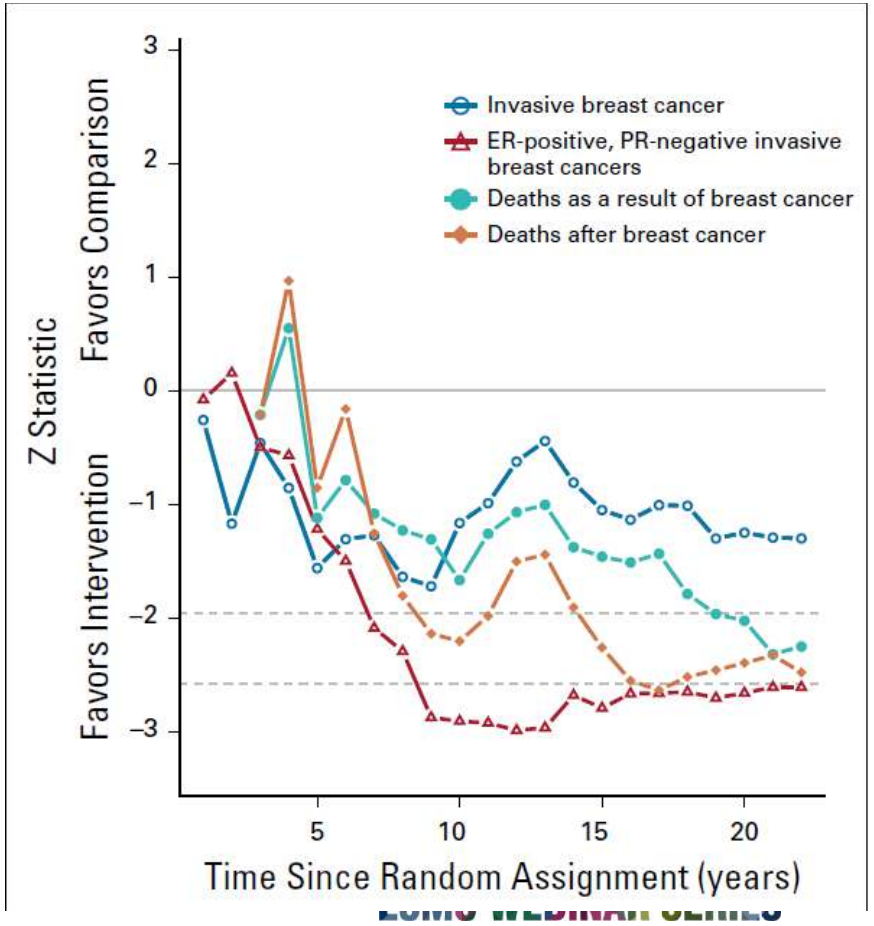
A major prospective study: Women's Health Initiative (WHI) Dietary Modification (DM)

Intervention = low-calorie, low-fat diet versus standard diet

Co-primary end points = incident invasive breast cancer and colorectal cancer, to be analysed separately.

Risk of death from breast cancer
HR, 0.79; 95% CI, 0.64 to 0.97





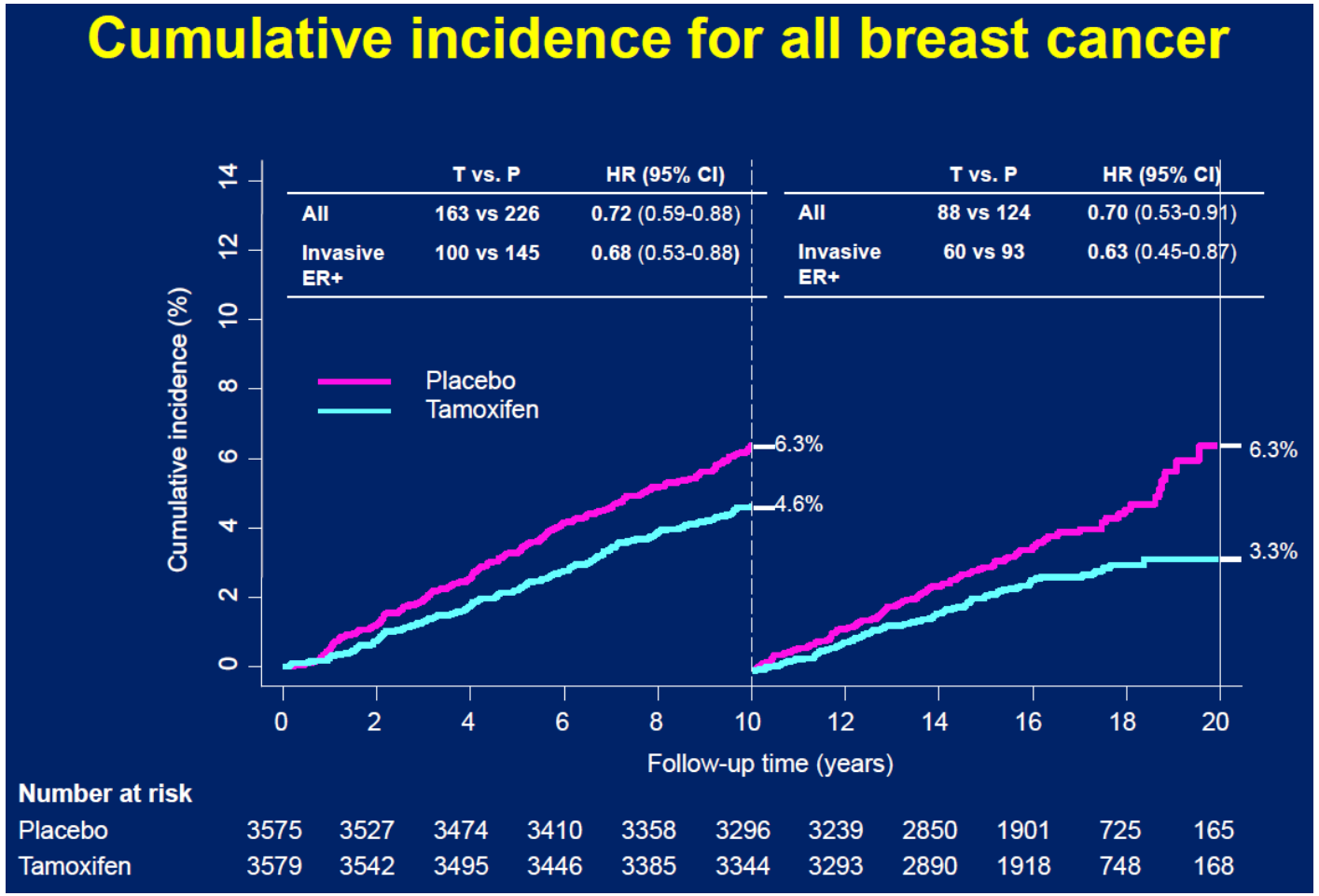
Chlebowski J Clin Oncol 2020

A NUTRITIONAL INTERVENTION COULD HAVE MORE EFFECT ON BC MORTALITY THAN ENDOCRINE TREATMENTS!!

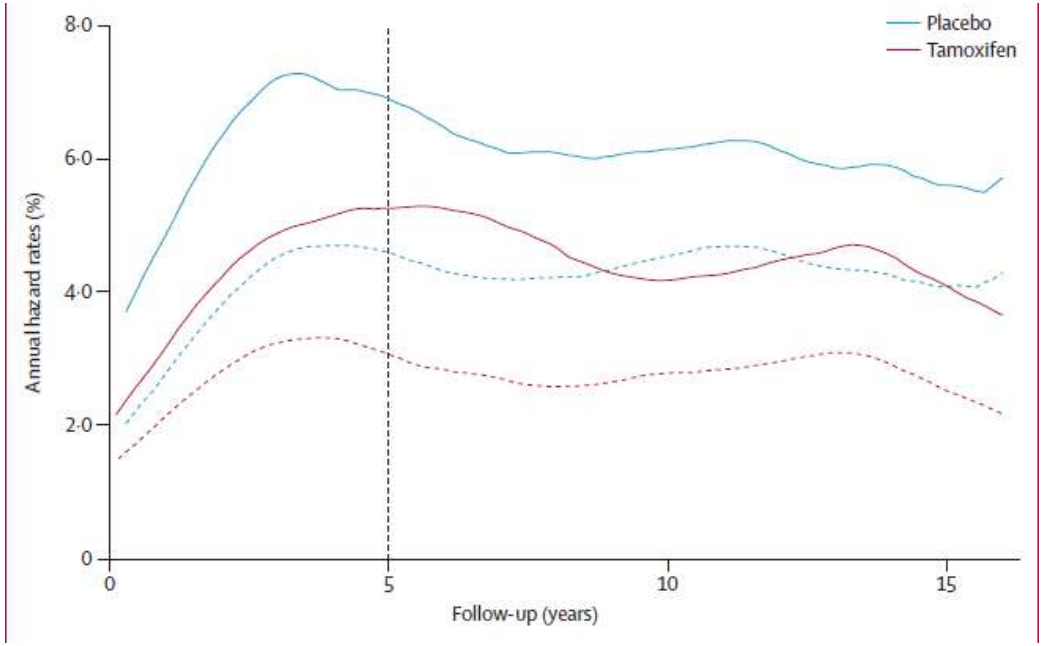
			Breast Cancer Incidence			Deaths From Breast Cancer		
Trial	**N**	**Follow-up[a]**	**Tamoxifen**	**Placebo**	**RR (95% CI)**	**Tamoxifen**	**Placebo**	
Royal Marsden[b]	2,494	13.2 years	82	104	0.78 (0.58 to 1.04)	12	9	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
NSABP P-1	13,388	74 months (mean)	145	250	0.57 (0.46 to 0.70)	12	11	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
IBIS-1	7,154	16.0 years (median)	251	350	0.71 (0.60 to 0.83)	31	26	1.19 (0.68 to 2.10)
			Anastrozole	**Placebo**	**HR (95% CI)**	**Anastrozole**	**Placebo**	
IBIS-II	3,864	131 months (median)	85	165	0.51 (0.39 to 0.66)	2	3	Not reported
			Exemestane	**Placebo**	**HR (95% CI)**	**Exemestane**	**Placebo**	**HR (95% CI)**
MAP.3	4,560	35 months (median)	11	32	0.35 (0.18 to 0.70)	1	0	Not reported
			Low-fat	**Control**	**HR (95% CI)**	**Low-fat**	**Control**	**HR (95% CI)**
WHI DM	48,835[a]	19.6 years (median)	1,299 (0.44%)	2,075 (0.46%)	0.95 (0.89 to 1.02)	132 (0.037%)	251 (0.047%)	0.79 (0.64 to 0.97)
			CEE	**Placebo**	**HR (95% CI)**	**CEE**	**Placebo**	**HR (95% CI)**
WHI CEE-alone	10,739	20.3 years (median)	238 (0.30%)	296 (0.37%)	0.78 (0.65 to 0.93)	30 (0.031%)	46 (0.046%)	0.60 (0.37 to 0.97)

Chlebowski et al, J Clin Oncol 2020, JOP 2021

A MODEL FOR BREAST CANCER INTERCEPTION: LONG-TERM EFFECT OF 5 YEARS OF TAMOXIFEN IN THE IBIS-1 STUDY



Reprogramming breast tissue?



Cuzick et al Lancet Oncol 2015; SABCS 2023

LIFESTYLE CHANGES: IS PREVENTION POSSIBLE?

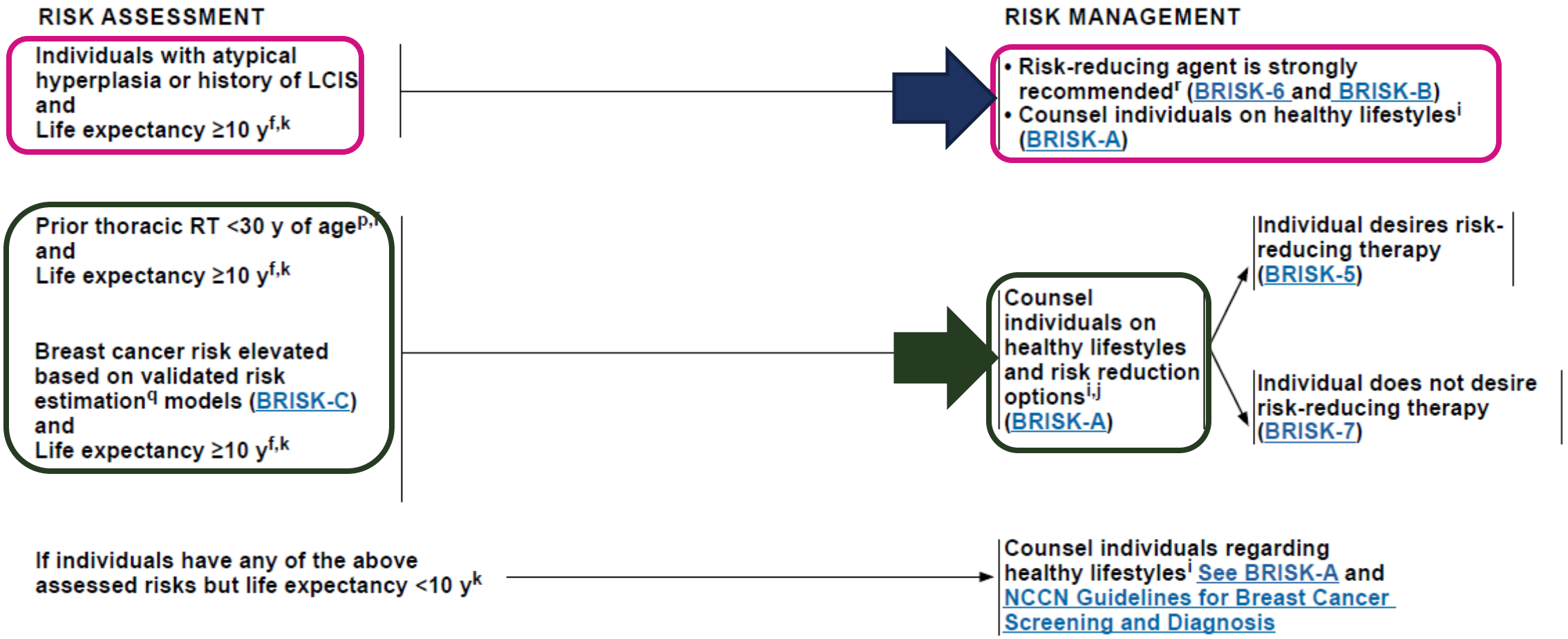
Towards stratified/personalized breast cancer prevention

- How does it work?
- Epidemiological data
- Interventional results
- How and for whom?
- Conclusions

INTERNATIONAL RECOMMENDATIONS FOR WOMEN AT HIGHER RISK OF BREAST CANCER: NCCN 2024

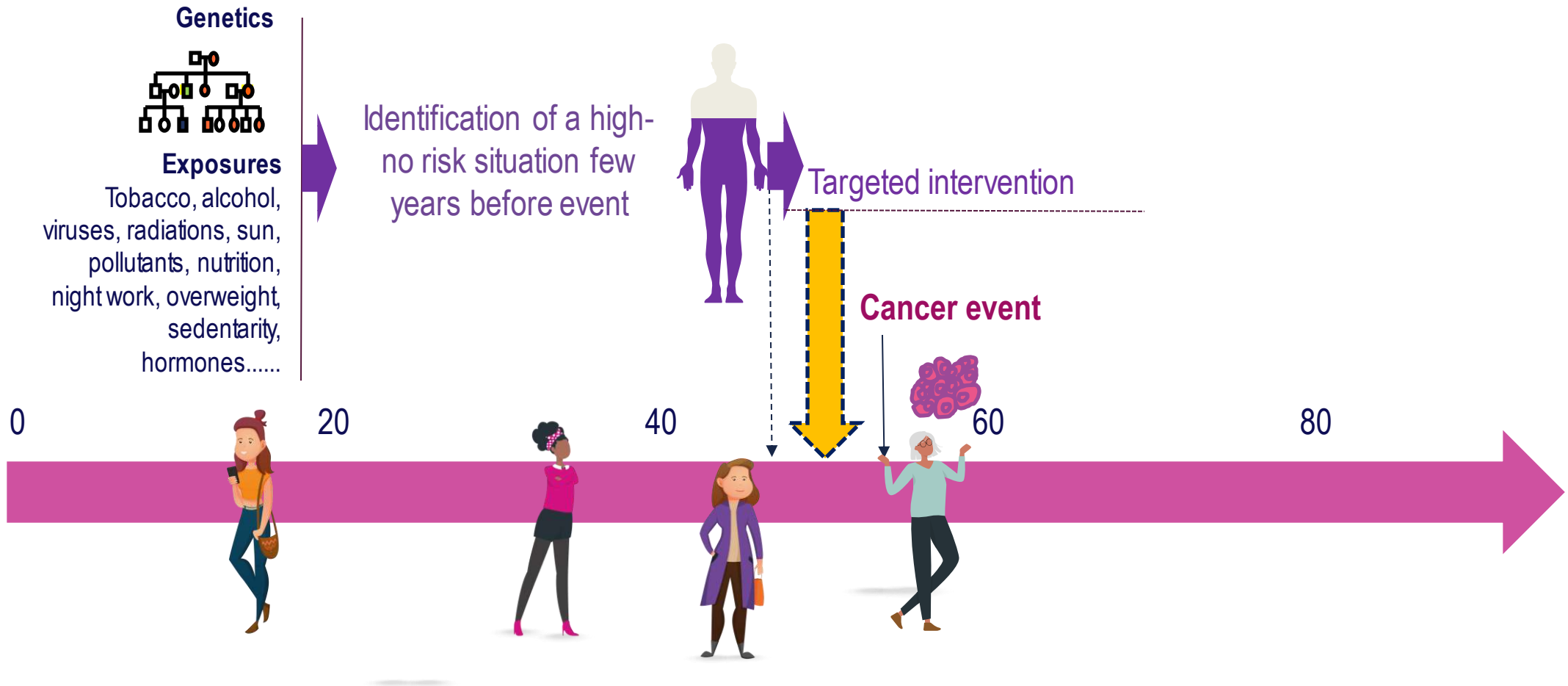
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Breast Cancer Risk Reduction



HOW TO DELIVER THIS PREVENTION?

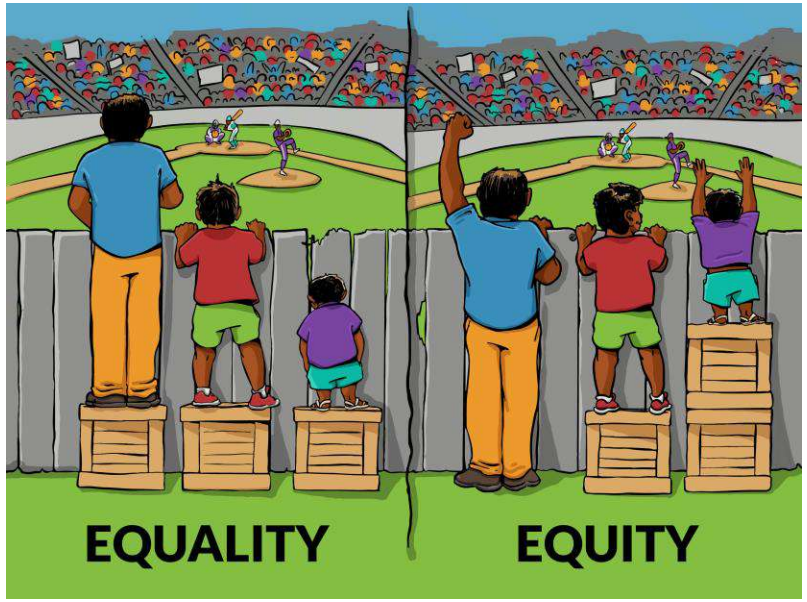
BEYOND GENERAL INTERVENTIONS: PERSONALISED RISK REDUCTION FOR HIGH RISK INDIVIDUALS



Suzette Delaloge

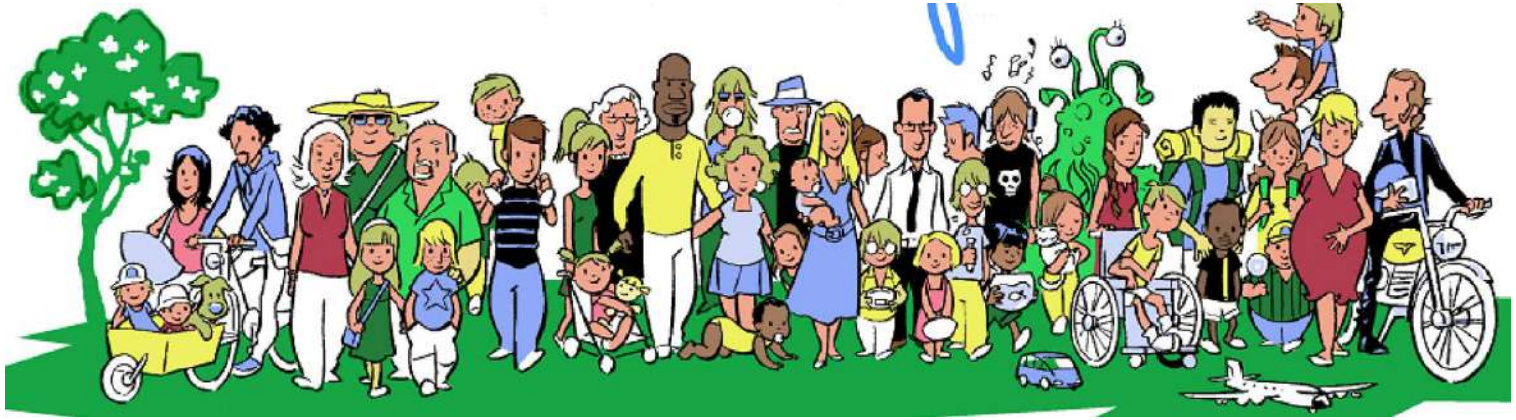
HOW TO DELIVER PREVENTION / RISK REDUCTION? THREE MAJOR ISSUES

Equitable interventions are absolutely necessary!



Beware of short-sightedness : biomarkers and intermediate objectives are instrumental

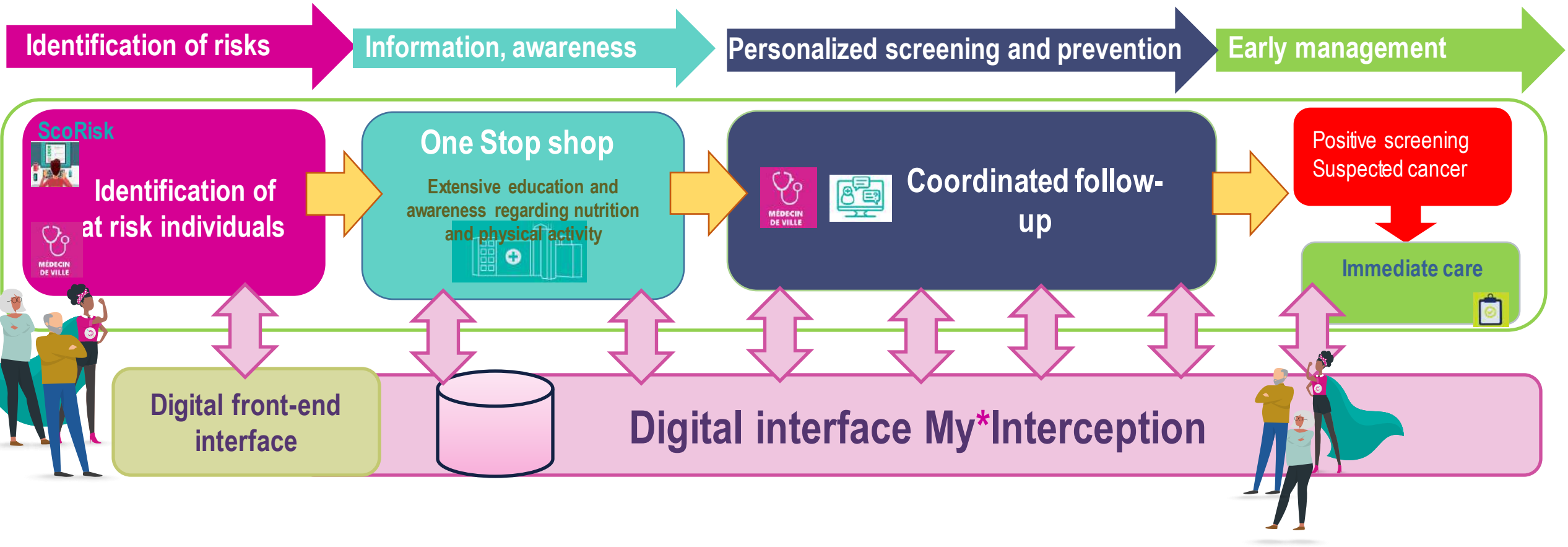
Take the environment into account



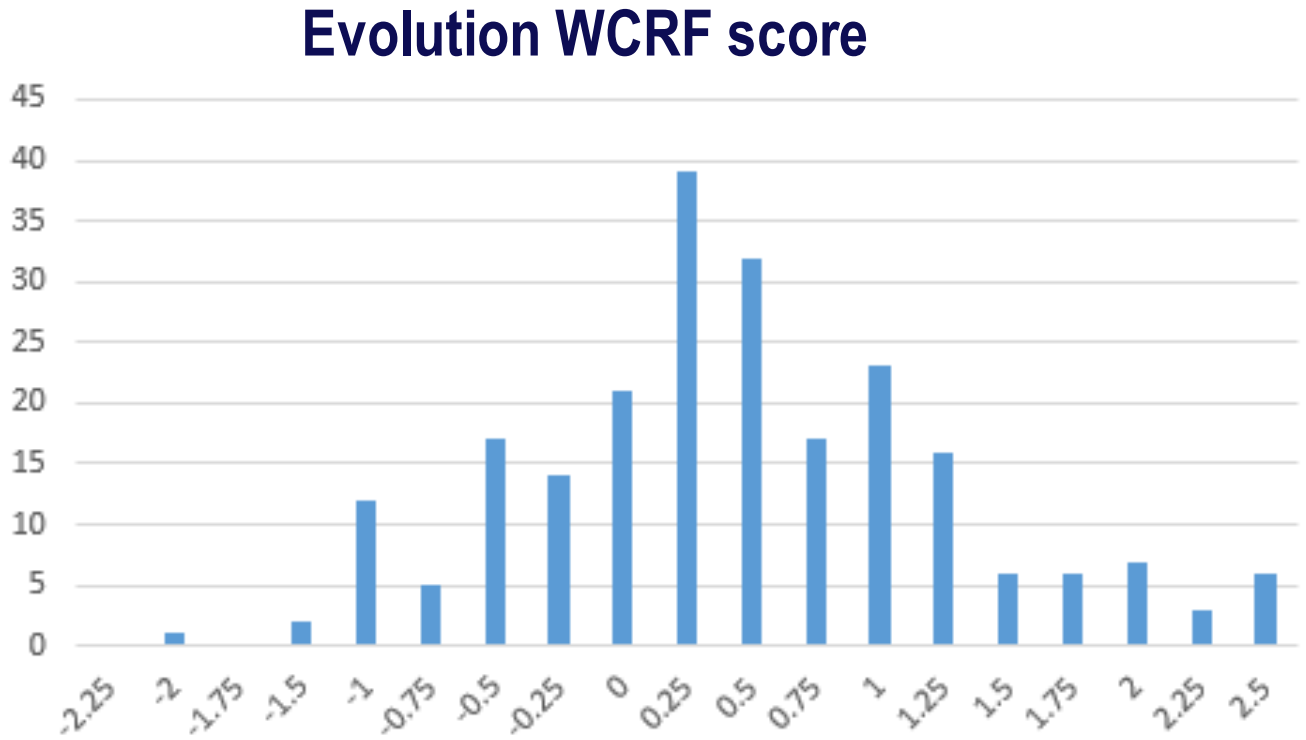
NEED FOR DEDICATED HEALTH CARE PREVENTION PATHWAYS

INTERCEPTION
GUSTAVE ROUSSY
Le programme de prévention personnalisée des cancers

The full pathway includes 4 indivisible pillars:



EARLY RESULTS OF THE INTERCEPTION PROGRAMME: 1-YEAR IMPROVEMENT IN WCRF PROFILE



N=324 respondents at 1 year

30% gained 1 WCRF point

LIFESTYLE CHANGES: IS PREVENTION POSSIBLE?

Towards stratified/personalized breast cancer prevention

- How does it work?
- Epidemiological data
- Interventional results
- How and for whom?
- Conclusions

Conclusions

- Up to 25% breast cancers avoidable trhough lifestyle modifications
- Lifestyle exposures including BMI, nutritional profile and physical activity are targets of interest for breast cancer prevention both in the general population, and among women at increased risk
- Translating from the immense amount of epidemiological data and interventions is not obvious....
- Personalised prevention of breast cancer is emerging
- Simple risk-reduction measures associated with strong levels of evidence are good achievable targets associated with demonstrated benefits ☺

Networks and care pathways

INTERCEPTION
GUSTAVE ROUSSY
Le programme de prévention personnalisée des cancers

THANK YOU!

Our funders and sponsors

International research networks

MyPeBS
Personalising Breast Screening

ONCOBIOME
Microbiota against cancer International research program

PREVALUNG-EU

4IN THE LUNG RUN

Cancer Core Europe

Patient associations

Cancer Contribution

les seintinelles
contre le cancer, tous volontaires

PATIENTS en réseau

National CANCEPT prevention network

IOT

unicancer

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CNGE

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UMR 981
UMR 1015
UMR 1018

LA LIGUE CONTRE LE CANCER

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ESMO DEEP DIVE: BREAST CANCER

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BREAST CANCER

EMERGING DATA ON HOW TO DEAL WITH HEREDITARY RISK

Shani Paluch-Shimon, MBBS, MSc

Hadassah University Hospital
Jerusalem, Israel

Hadassah University Hospital

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DECLARATIONS OF INTEREST

Roche: Speakers bureau, honoraria, consultancy, travel

Astra Zeneca: Speakers bureau, honoraria, consultancy

Novartis: Speakers bureau, honoraria, consultancy

Pfizer: Speakers bureau, honoraria, consultancy

Lilly: Speakers bureau, honoraria, consultancy

MSD: Speakers bureau, honoraria, consultancy

Exact Sciences/Rhenium: Speakers bureau, honoraria

Gilead: Consultancy, speakers bureau

Stemline: Consultancy

BACKGROUND

Germline pathogenic variants (PV) in ~6*-17^% of contemporary breast cancer (BC) cohorts

Most common germline PVs amongst patients with BC – *BRCA1, BRCA2*

BRCA1/2 pathogenic variants (PV) - ↑ prevalence in younger women with BC, TNBC, FHx of BC or Ovarian cancer (+ other malignancies) and in certain ethnic groups (Ashkenazi Jewish)

A PV in *BRCA1/2* confers a lifetime risk of 35-90% of BC

What we find in terms of hereditary predisposition genes including prevalence will depend on where we look (cohort):

- Age – *BRCA1/2* – higher prevalence of early onset breast cancer
- Subtype
- Stage of disease
- Ethnicity

BC=Breast Cancer TNBC=Triple Negative Breast Cancer PV=pathogenic variant

Tung et al JCO 2016; Rosenberg et al, JAMA Onc 2016; Kuchenbacker et al JAMA 2017

THE CHALLENGE

"Other" non-*BRCA1/2* moderate-high penetrance genes

↑ use of multi-gene germline panel tests - ↑ identification of other moderate-high penetrance genes

↑ use of genomic testing in ABC - ↑ identification of germline pathogenic variants

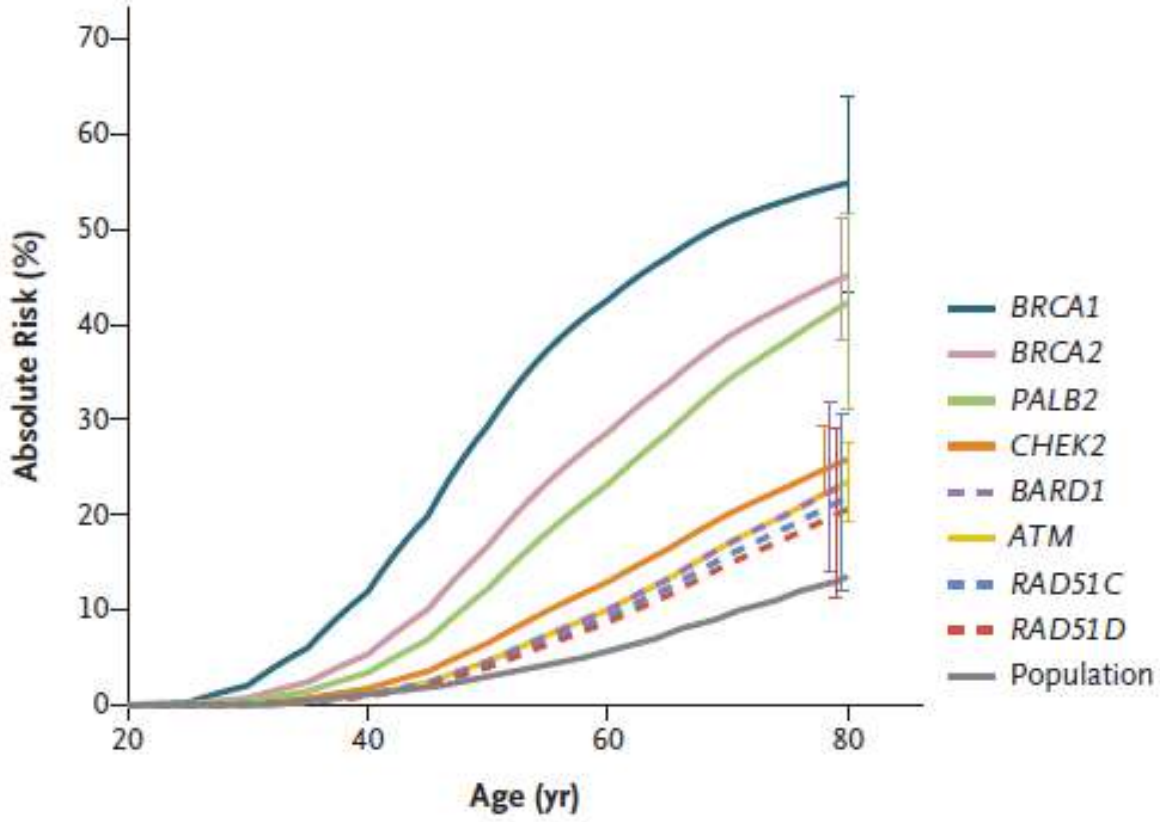
For non-*BRCA1/2* moderate-high penetrance genes – limited data or evidence on:

- Screening
- Appropriate risk-reducing measures
- Optimal oncological management – surgery, systemic treatment, radiotherapy

For non-*BRCA1/2* moderate-high penetrance genes – limited yet growing body of data on phenotype and disease course

BACKGROUND

Lifetime risk of breast cancer



BCAC, NEJM, 2021; Hu et al, NEJM, 2021

Cumulative Breast Cancer Risk amongst *BRCA1/2* mutation carriers

Table 2. Breast and Ovarian Cancer Incidence Rates Per 1000 Person-Years, Kaplan-Meier Estimates of the Cumulative Risks, and Standardized Incidence Rates by 10-Year Age Groups

Age, During Follow-up, y[a]	No. of Women Contributing in Age Category[a]	No. of Person-Years	No. of Events	Incidence per 1000 Person-Years (95% CI)	Cumulative Risk, % (95% CI)[b]	Standardized Incidence Rate (95% CI)[c]
Breast Cancer						
BRCA1 mutation carriers						
≤20	53	74.0	0	0		
21-30	605	2222.5	13	5.9 (3.4-10.1)	4 (2-7)	73.7 (42.9-126.8)
31-40	1048	3831.6	90	23.5 (19.1-28.9)	24 (21-29)	46.2 (37.3-57.1)
41-50	870	3317.8	94	28.3 (23.1-34.7)	43 (39-48)	17.2 (14.0-21.2)
51-60	479	1905.9	49	25.7 (19.4-34.0)	56 (51-61)	9.7 (7.2-12.9)
61-70	201	761.3	19	25.0 (15.9-39.1)	66 (61-72)	7.0 (4.5-11.0)
71-80	55	243.0	4	16.5 (6.2-43.9)	72 (65-79)	4.8 (1.8-12.8)
Total	2276[d]	12356.1	269	21.8 (19.3-24.5)		16.6 (14.7-18.7)
BRCA2 mutation carriers						
≤20	30	44.0	0	0		
21-30	329	1046.0	5	4.8 (2.0-11.5)	4 (2-9)	60.8 (25.5-144.9)
31-40	625	2136.1	23	10.8 (7.2-16.2)	13 (9-19)	20.3 (13.5-30.5)
41-50	669	2365.0	65	27.5 (21.6-35.1)	35 (29-41)	16.4 (12.9-20.9)
51-60	384	1437.2	44	30.6 (22.8-41.1)	53 (46-59)	11.4 (8.4-15.5)
61-70	174	610.2	14	22.9 (13.6-38.7)	61 (55-68)	6.4 (3.8-10.7)
71-80	68	274.6	6	21.9 (9.8-48.6)	69 (61-77)	6.6 (3.0-14.7)
Total	1610[d]	7913.1	157	19.8 (17.0-23.2)		12.9 (11.1-15.1)

CI, confidence interval

Kuchenbacker, JAMA 2017

Average estimated cumulative lifetime breast cancer risks

	Population	BRCA1	BRCA2	ATM	CHEK2 (1100delC)	CHEK2 (I157T)	PALB2
<40	0.5%	24%	13%	1.4%	1.5%	0.8%	4%
40-49	2%	43%	35%	5.6%	5.9%	3.2%	14%
50-59	4.4%	56%	53%	11.8%	12.6%	6.8%	26%
60-69	8%	66%	61%	20.8%	22.1%	12.3%	35%
CLTR (80)	12%	72%	69%	30%	31.8%	18.3%	44%

Tung et al, Nature Rev Clin Oncol, 2016;
Kuchenbaeker, JAMA 2017

LIFETIME CANCER RISK IN HBOC ASSOCIATED PV

Table 1. Lifetime cancer risks in HBOC-associated PVs

	Breast cancer[a]	Tubo-ovarian cancers[b]	Pancreatic cancer[c]	Colon cancer[d]	Other cancers
ATM	Yes 25%-30%	Yes ≤5%	Yes <5%	No	Prostate 30%
BARD1	Yes ~20%	No	No	No	No
BRCA1	Yes >60%	Yes 40%-60%	Yes <5%	No	
BRCA2	Yes >60%	Yes 15%-30%	Yes <5%	No	Prostate 33%
BRIP1	No	Yes 5%-10%	No	No	No
CDH1	Yes (LBC) 40%	No	No	No	Diffuse gastric cancer 35%-45%
CHEK2	Yes 25%-30%	No	No	Yes 15%	
PALB2	Yes 40%-60%	Yes 3%-5%	Yes 2%-3%	No	No
PTEN	Yes 40%	No	No	Yes 10%	Thyroid 20%; endometrial 20%
RAD51C	Yes 20%	Yes 10%	No	No	No
RAD51D	Yes 10%	Yes 10%	No	No	No
STK11	Yes 40%	No	Yes 10%-30%	Yes 30%	Gastric 30%; Sertoli-Leydig 10%-20%
TP53	Yes 40%	No	Possibly	Possibly	Sarcoma, brain, leukaemia, adrenocortical carcinoma

HBOC=hereditary breast & ovarian cancer syndrome; PV=pathogenic variant

Sessa….Paluch-Shimon, Annals of Oncology, 2023

HEREDITARY BREAST CANCER SYNDROME – HOW DOES THIS CHANGE PATIENT MANAGEMENT?

Risk management- screening & risk reducing measures (individual, family, population)

Local management

- Lumpectomy vs mastectomy
- Bilateral mastectomy?

Systemic therapy

- Early breast cancer – PARP inhibitors
- Advanced breast cancer –*BRCA1/2, PALB2* – PARP inhibitors, platinum agents

Reproductive considerations

Ongoing follow-up & survivorship

IMPORTANT CONSIDERATIONS

Different genes, different risks, different management

- Not all HBOC syndromes are created equal – different gene PVs, different risks
- HBOC syndromes can be divided into high risk & low-moderate risk – the approach to screening and risk-reduction should be tailored according to risk combined with family history
- Validated risk assessment tools (such as CanRisk (https://www.canrisk.org/) may be used to aid individual risk management [C]
- Risk-reducing mastectomy is most beneficial in women with a high risk PV
- Frequency and modality of breast imaging will be different for the different HBOC syndromes
- RRBSO should not be performed unless there is an associated ovarian cancer risk or a therapeutic indication, and should not be performed earlier than clinically indicated – it has far reaching impact on women's health!!

ESMO DEEP DIVE: BREAST CANCER

INDIVIDUALIZING RISK

INDIVIDUALIZING RISK

Same mutation, different individual, different risk

To tailor risk assessment eed to:

- Incorporate risk factors – family history, mammographic breast density, reproductive factors, polygenic risk score
- Use of validated risk prediction models & tools:

  www.Canrisk.org

- Risk management should be individualised and, when available, validated tools should be used to aid decision making [B].

Sessa….Paluch-Shimon, Annals of Oncology, 2023

What is CanRisk?

CanRisk is an online tool that enables healthcare professionals to calculate an individual's future risks of developing *breast and ovarian cancer* using cancer family history, genetic and other risk factors. CanRisk also calculates mutation carrier probabilities in breast and ovarian cancer susceptibility genes.

CanRisk

> Start CanRisk

What does CanRisk do?

CanRisk uses the *BOADICEA* v6 model to calculate breast and ovarian cancer risks based on information entered for the individual which can include personal risk factors, cancer family history, genetic testing for high- and moderate-risk genes, polygenic scores and mammographic density (click to see what information is used). It presents the cancer risks in textual and graphical formats to assist the communication of

Who is CanRisk for?

CanRisk is designed for use by healthcare professionals to help them communicate and discuss breast and ovarian cancer risk with their patients.

Endorsements

- NICE | The National Institute for Health and Care Excellence
  - Breast Cancer
  - Ovarian Cancer
- UK Cancer Genetics Group guidelines
- Ontario Breast Screening program
- eviQ Australian guidelines for health professionals
- NCCN | National Comprehensive Cancer Network

POLYGENIC RISK SCORE

- Combined risk from multiple risk inducing single nucleotide polymorphisms (SNPs) from GWAS studies
- Explain approximately 30% of breast cancer hereditability
- Combined with other risk factors & risk prediction models can help tailor risk estimates

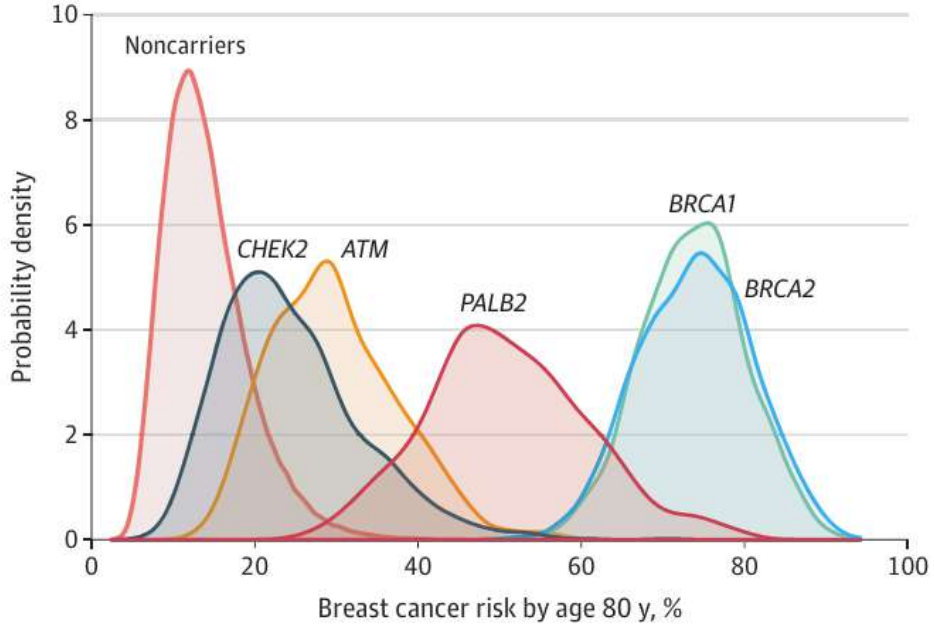
  Example – study by Gao et al – was able to classify >30% of *CHEK2* & 50% of *ATM* carriers with an estimated lifetime risk <20%
- Limitations? Most GWAS studies on women >50 and Caucasian
- Challenges? Communicating risk

GWAS=genome wide association studies

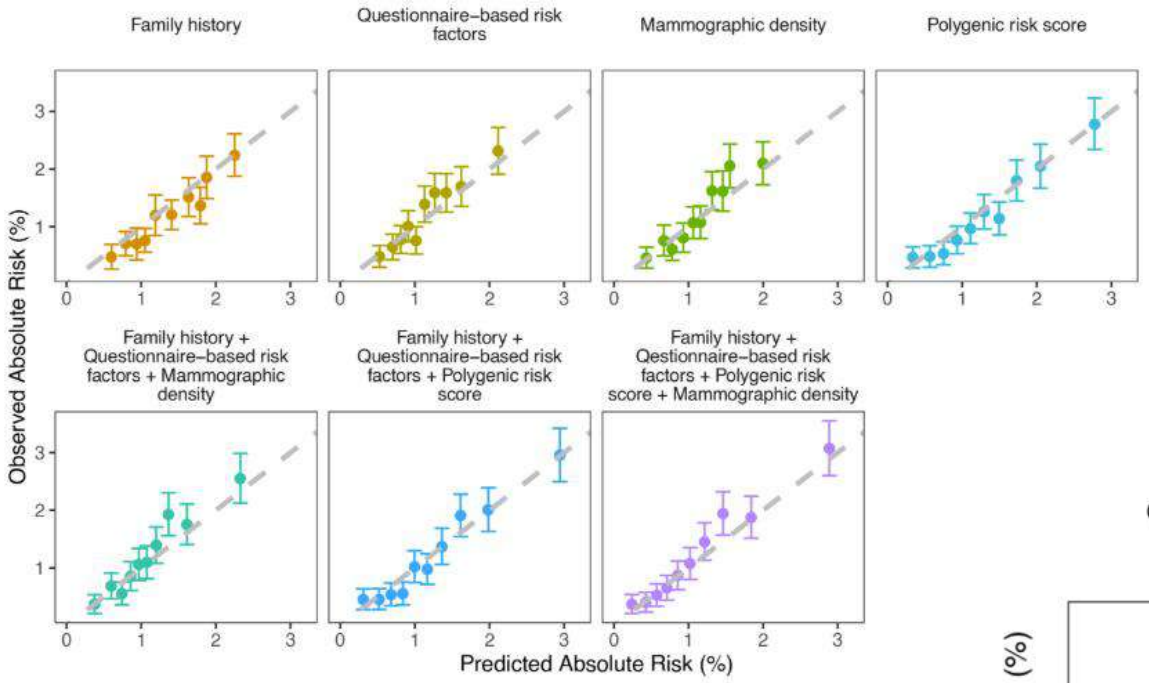
Gao et al, JCO, 2021, Roberts et al, The Breast, 2023

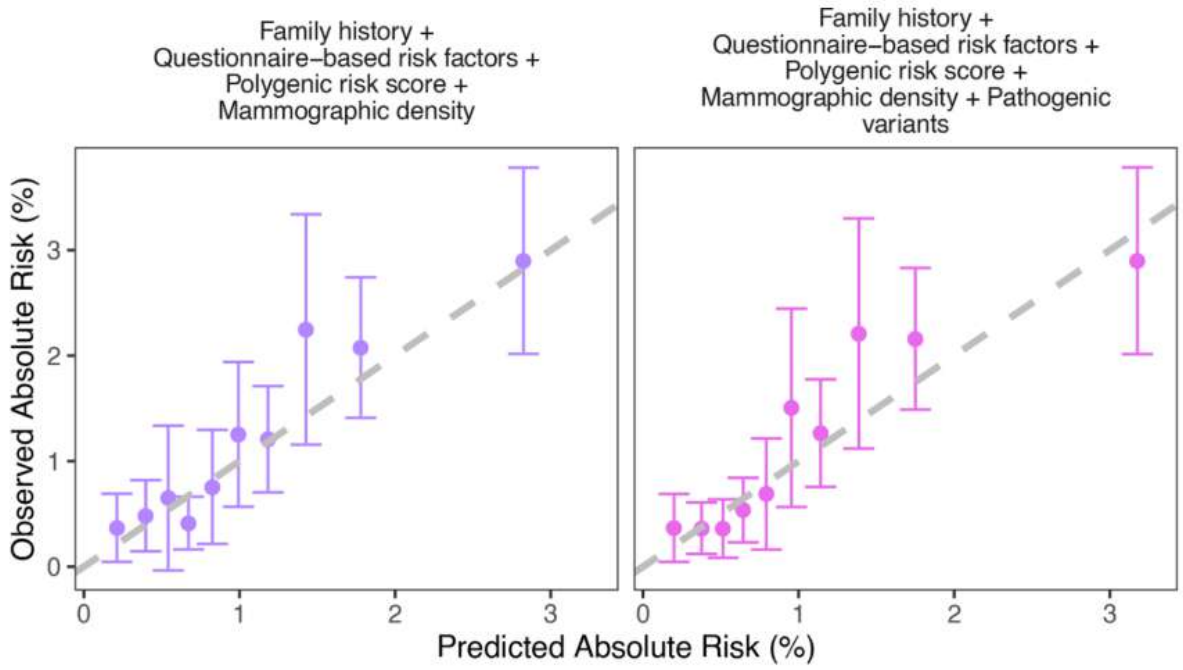
POLYGENIC RISK SCORE

Figure. Modification of Lifetime Breast Cancer Risk for Pathogenic Variant Carriers and Noncarriers by an 86-Single-Nucleotide Variant Score



Gallagher et al, JAMA network open, 2020





Yang et al, Journal of Med Genetics, 2022

INDIVIDUALIZING RISK

Penetrance and prognosis can differ between different types of PVs

- Missense PVs in both functionally important domains (RING and BRCT) in *BRCA1* are associated with lower risks of BC than protein truncating (PTC) variants

  - Cumulative risk by age 70 for *BRCA1* PTC was 70% compared with a missense PV in the BCRT domain

  - Differences less pronounced in *BRCA2*, but slightly lower risk for missense mutations in families where Dx was >50yro

  - For women >50 at Dx with a *BRCA* missense PV – risk level similar to moderate penetrance PVs

Li et al, Genet Med, 2023

ESMO DEEP DIVE:
BREAST CANCER

SCREENING & RISK REDUCTION

INTENSIFIED SCREENING FOR BREAST CANCER

- Women with HBOC should be offered intensified screening if they do not opt for RRM [A].
- Breast MRI should be considered the essential component of intensified screening programmes [A].
- In the presence of a *BRCA1*, *BRCA2* or *PALB2* PV intensified screening should start at age 30, or 5 years younger than the youngest family member with breast cancer [A].
- Annual screening intervals are recommended, except for *BRCA1*, where 6-monthly screening should be considered [A].
- If half-yearly screening is considered, this may be best achieved by annual MRI and, depending on availability, resources and local guidelines, the following imaging may be considered in between annual MRI studies:
  - in carriers 30-39 years of age, ultrasound with or without mammography [C]
  - in carriers ≥ 40 years of age, mammography with or without ultrasound [C]

RRM=risk reducing mastectomy

INTENSIFIED SCREENING FOR BREAST CANCER

- Women with PVs in *ATM*, *BARD1*, *CHEK2* (truncating), *RAD51C* or *RAD51D* should have comprehensive assessment of breast cancer risk to determine eligibility for breast MRI [C].
- In the presence of *CDH1*, *PTEN* or *STK11* PVs, intensified breast screening should start at age 30, or 5 years younger than the youngest family member with breast cancer and from age 20 for *TP53* [A].

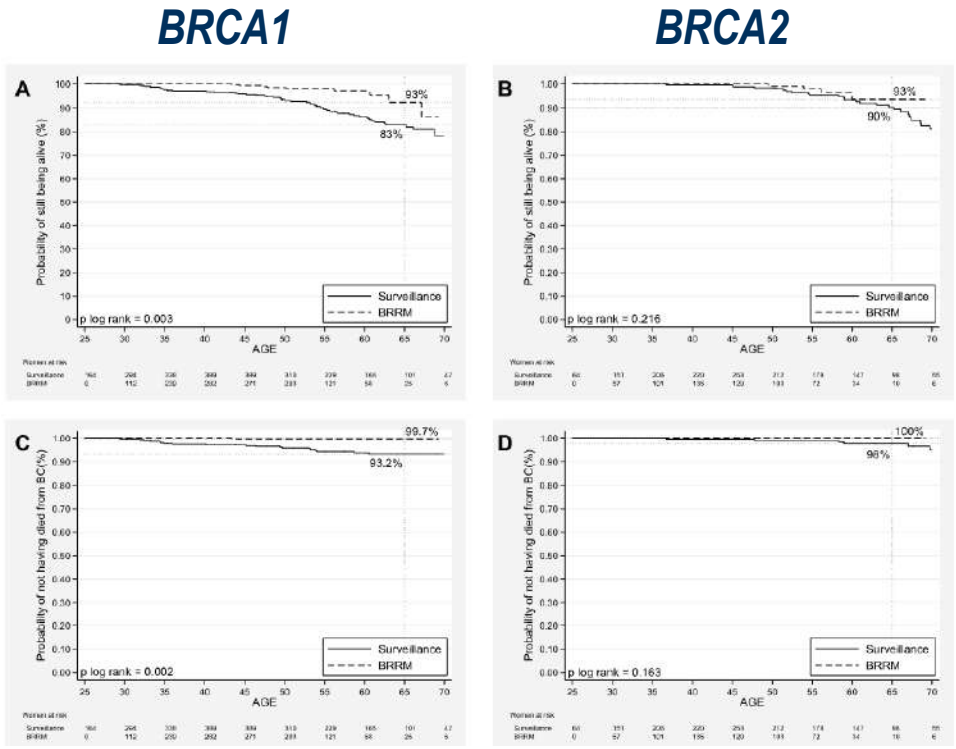
RISK REDUCING SURGERY – BREAST CANCER

- BRRM is the most effective method for reducing breast cancer risk for *BRCA1/2* carriers and should be discussed in the context of individually tailored decision making [B].
- BRRM should be discussed in carriers of other high-risk genes alongside family history – *TP53*, *PTEN*, *STK11*, *CDH1* and *PALB2* [C].
- NSM is a reasonable alternative to TM [C].
- Immediate reconstruction is safe and should be offered [C].
- In women with stage I-III high-risk PV-associated breast cancer (not including *TP53*), breast-conservation with therapeutic radiation is a safe alternative to RRM. RRM should be considered within the context of disease prognosis, risks and benefits, and patient preference [C].

BRRM=bilateral risk-reducing mastectomy; NSM-nipple-sparing mastectomy; TM=total mastectomy; PV=pathogenic variant

RISK REDUCING MASTECTOMY – UNAFFECTED CARRIERS

- Conflicting data whether risk reducing mastectomy impacts survival in unaffected carriers



Heemskerk-Gerritsen et al, BCRT, 2019

RISK REDUCING MEDICATION IN *BRCA* CARRIERS

Tamoxifen

- NSABP-P1 sub-study – too small to draw conclusions
- Some retrospective studies suggesting benefit
- Self-reporting study on Tamoxifen use – suggested reduced risk of BC in BRCA carriers

Aromatase inhibitors

- LIBER study – under-powered – no benefit of Letrozole vs placebo
- Retrospective study, in women with BC, aromatase inhibitors reduce the risk of CBC in BRCA carriers

No data in non-BRCA pathogenic variants,
strong rationale exists – for example ATM & CHEK2 mostly associated wit hormone positive breast cancers!

King et al, JAMA 2001; Phillips et al, JCO, 2013; Shafaee et al, BCRT, 2022; Pujol et al, JCO 2020; Kostopoulos, BRT, 2023

OVARIAN CANCER RISK-REDUCTION

- The most effective strategy for ovarian cancer risk reduction in *BRCA1/2* PV carriers is RRBSO [A].
- RRBSO should be carried out in women who have completed childbearing, at age 35-40 for *BRCA1* PV carriers and at age 40-45 for women with *BRCA2* PVs. Timing of surgery should take into consideration family history [B]
- Risk-reducing salpingectomy (bilateral salpingectomy alone or bilateral salpingectomy followed by delayed oophorectomy) are not recommended outside the setting of a clinical trial [C].
- RRBSO should be considered in women who have completed childbearing who are carriers of PVs in *BRIP1*, *RAD51C*, *RAD51D* at age 45-50. RRBSO may be considered for post-menopausal women with a *PALB2* PV [C].

PV=pathogenic variant, RRBSO=risk-reducing bilateral salpingo-oophorectomy

OVARIAN CANCER RISK-REDUCTION

- The PV type, patient's preferences and family history should be taken into consideration when deciding the timing of RRBSO.
- It should be delayed until an age when ovarian cancer risk is increased above that of the general population.
- Performing RRBSO before the necessary age can have a negative impact on a woman's health including all the consequences of premature menopause (increased risk of osteoporosis, cognitive dysfunction, cardiovascular disease and early mortality) thus appropriate timing is critical.

PV=pathogenic variant , RRBSO=risk-reducing bilateral salpingo-oophorectomy

ESMO DEEP DIVE:
BREAST CANCER

MANAGEMENT OF RISK IN AFFECTED CARRIERS

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BCS vs Mastectomy

- BCS is a legitimate and safe choice
- Therapeutic radiation is safe:
  - Reduces local ipsilateral recurrence
  - Does not increase contra-lateral disease
- Contralateral radiation?

Prophylactic irradiation to the contralateral breast for *BRCA* mutation carriers with early-stage breast cancer

E. Evron[1,2†], A. M. Ben-David[3,4†], H. Goldberg[5†], G. Fried[6], B. Kaufman[3,4], R. Catane[3,4], M. R. Pfeffer[7], D. B. Geffen[8,9], P. Chernobelsky[8†], T. Karni[10], R. Abdah-Bortnyak[6], O. Rosengarten[11], D. Matceyevsky[12], M. Inbar[7], A. Kuten[6] & B. W. Corn[11*]

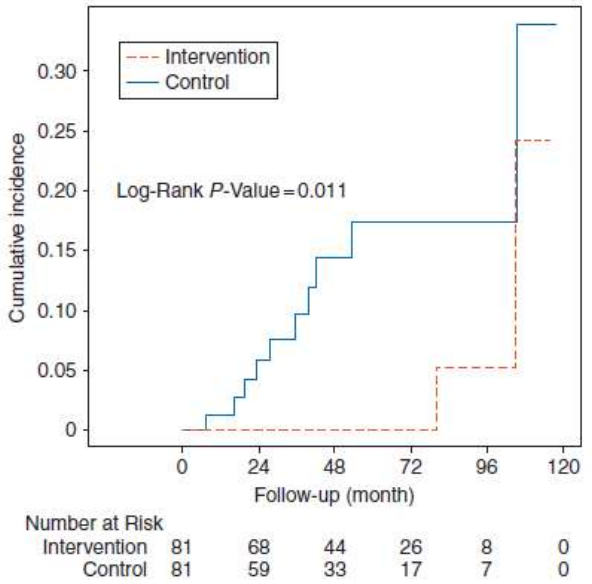
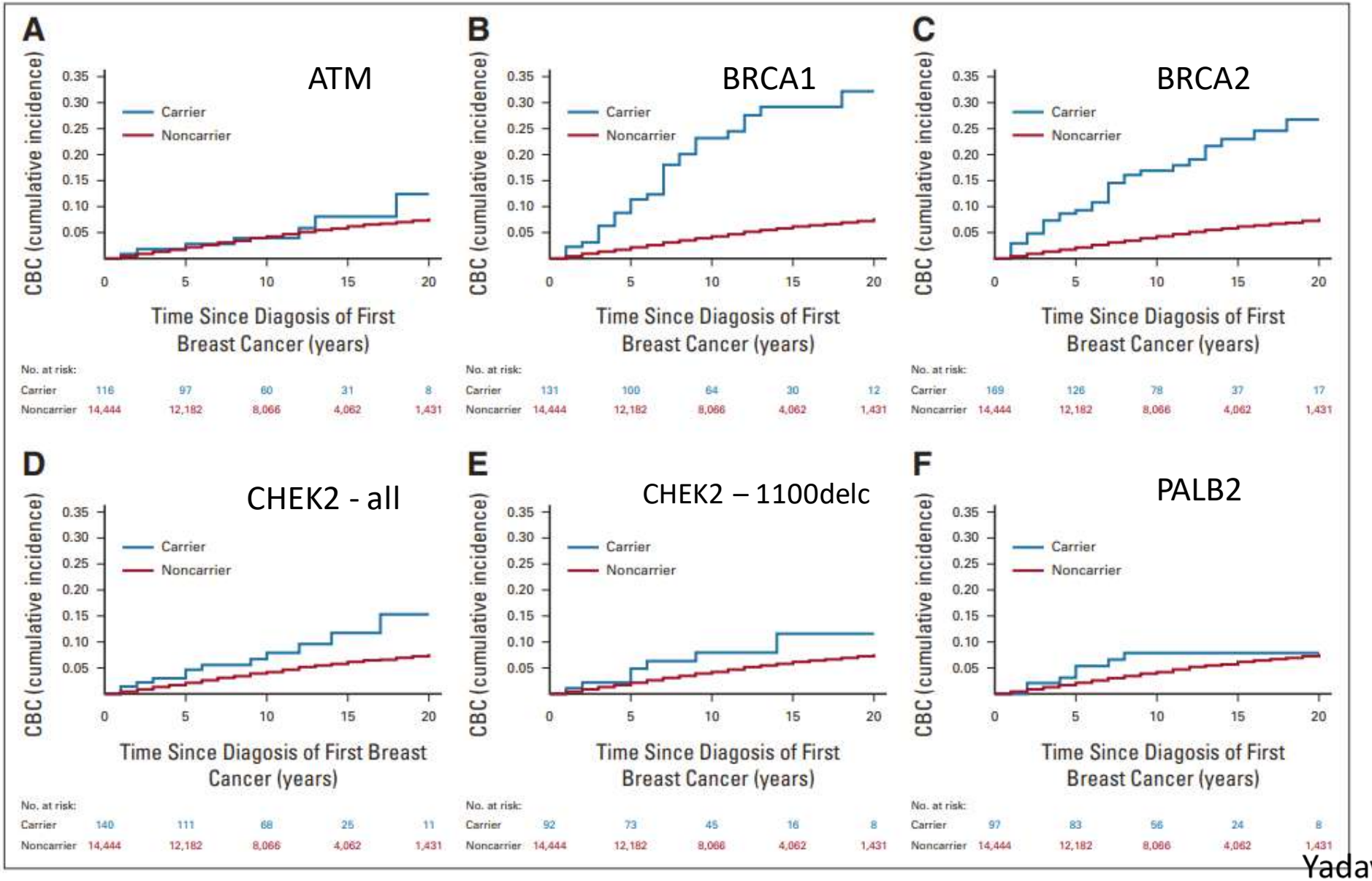


Figure 1. Cumulative incidence of contralateral breast cancer as a first event.

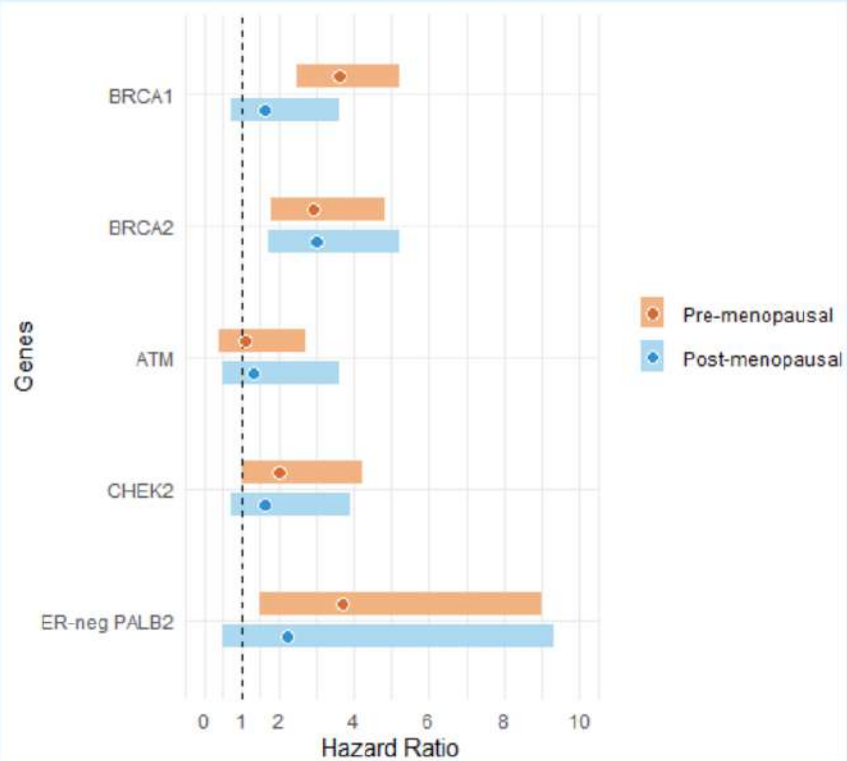
- Contralateral mastectomy – some studies suggest that there may be a long term survival benefit
- **Decision must be tailored to individual's needs**

Risk of contralateral breast cancer?



Yadav et al, JCO, 2023

Contralateral Breast Cancer Risk by **Menopausal Status** at First Breast Ca Diagnosis



Adjusted Hazard Ratios

	10-year Cumulative Incidence of CBC*	
	Pre-menopausal	**Post-menopausal**
Non-carriers	5.8%	3.7%
BRCA1	33%	11%
BRCA2	27%	9.5%
ATM	2.9%	4.6%
CHEK2	13%	4.3%

*: Unadjusted analysis

Yadav et al, JCO, 2023

RISK OF CONTRALATERAL BC BY SUBTYPE & GERMLINE PV

TABLE 2. Contralateral Breast Cancer Risk Among Germline PV Carriers by ER Status

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No.	CBC	HR (95% CI)[b]	*P*	Total, No.	CBC	HR (95% CI)[b]	*P*	Total, No.	CBC	HR (95% CI)[b]	*P*
Noncarriers[c]	14,444	711	—	—	10,989	462	—	—	2,391	157	—	—
ATM	116	7	1.2 (0.6 to 2.6)	.56	92	5	1.4 (0.6 to 3.3)	.48	14	1	ND	ND
BRCA1	132	31	2.7 (2.0 to 3.8)	< .001	42	7	3.1 (1.7 to 5.6)	< .001	79	23	< .001	< .001
BRCA2	170	33	3.0 (2.1 to 4.3)	< .001	105	18	3.3 (2.0 to 5.5)	< .001	52	10	< .001	.002
CHEK2												
All PV[d]	140	12	1.9 (1.1 to 3.3)	.03	121	11	2.0 (1.1 to 3.5)	.02	12	1	ND	ND
c.1100delC	92	7	1.9 (0.9 to 3.8)	.07	79	7	2.2 (1.1 to 4.5)	.02	9	0	ND	ND
PALB2	97	7	1.3 (0.6 to 2.6)	.50	54	1	0.4 (0.1 to 2.8)	.37	33	6	2.9 (1.4 to 6.4)	.006

Yadav et al, JCO, 2023

RISK OF CONTRALATERAL BC BY GERMLINE PV, SUBTYPE & MENOPAUSAL STATUS

Premenopausal

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*
Noncarriers[c]	3,775 (93.1)	251	—	—	2,775 (93.9)	147	—	—	781 (90.8)	74	—	—
ATM	38 (0.9)	3	1.1 (0.4 to 2.7)	.87	31 (1.0)	1	ND	ND	2 (0.2)	1	ND	ND
BRCA1	70 (1.7)	25	3.6 (2.5 to 5.2)	< .001	26 (0.9)	7	4.8 (2.6 to 8.7)	< .001	41 (4.8)	18	3.5 (2.1 to 5.8)	< .001
BRCA2	71 (1.8)	21	2.9 (1.8 to 4.8)	< .001	47 (1.6)	13	3.4 (1.8 to 6.6)	< .001	19 (2.2)	7	3.3 (1.6 to 6.6)	< .001
CHEK2												
All PVs[d]	62 (1.5)	7	2.0 (1.0 to 4.2)	.06	54 (1.8)	7	2.5 (1.2 to 5.4)	.01	4 (0.5)	0	ND	ND
c.1100delC	40 (1.0)	5	2.5 (1.1 to 5.5)	.02	35 (1.2)	5	3.2 (1.4 to 7.3)	.007	3 (0.3)	0	ND	ND
PALB2	36 (0.9)	4	1.6 (0.6 to 4.1)	.33	20 (0.7)	0	ND	ND	13 (1.5)	4	3.7 (1.5 to 9.0)	.003

Postmenopausal

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*
Noncarriers[c]	10,669 (96.6)	467	—	—	8,214 (97.2)	322	—	—	1,610 (93.5)	83		
ATM	78 (0.7)	4	1.3 (0.5 to 3.6)	.58	61 (0.7)	4	1.8 (0.7 to 4.8)	.25	12 (0.7)	0	ND	ND
BRCA1	62 (0.6)	6	1.6 (0.7 to 3.6)	.24	16 (0.2)	0	ND	ND	38 (2.2)	5	2.3 (0.9 to 5.6)	.07
BRCA2	99 (0.9)	11	3.0 (1.7 to 5.2)	< .001	58 (0.7)	5	2.7 (1.1 to 6.5)	.03	33 (1.9)	3	2.6 (0.9 to 7.7)	.09
CHEK2												
All PVs[d]	78 (0.7)	5	1.6 (0.7 to 3.9)	.24	67 (0.8)	4	1.5 (0.7 to 3.8)	.45	8 (0.5)	1	ND	ND
c.1100delC	52 (0.5)	2	ND	ND	44 (0.5)	2	ND	ND	6 (0.3)	0	ND	ND
PALB2	61 (0.6)	3	1.0 (0.3 to 3.3)	.95	34 (0.4)	1	ND	ND	20 (1.2)	2	2.2 (0.5 to 9.3)	.28

Yadav et al, JCO, 2023

DOES CRRM IMPROVE SURVIVAL?

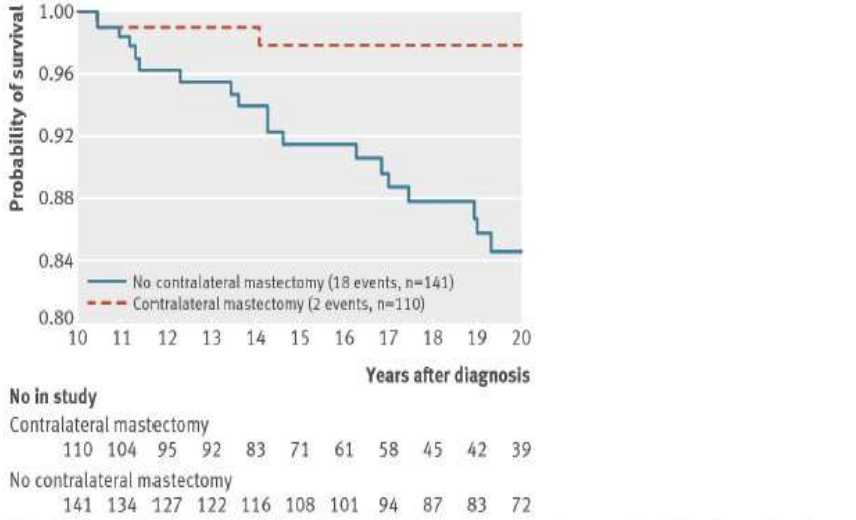


Fig 2 Survival from 10 to 20 years after breast cancer, by contralateral mastectomy

Stage 1 & 2 at Dx
Most were <50 at Dx

Metcalfe, BMJ, 2014

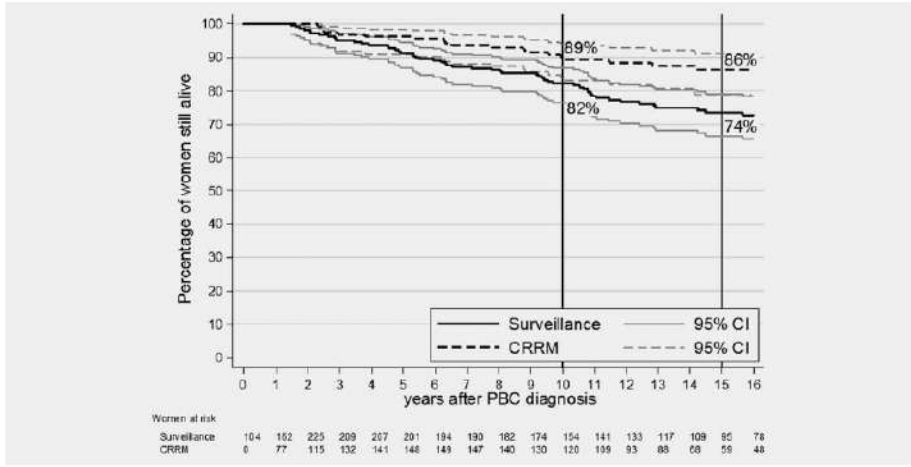
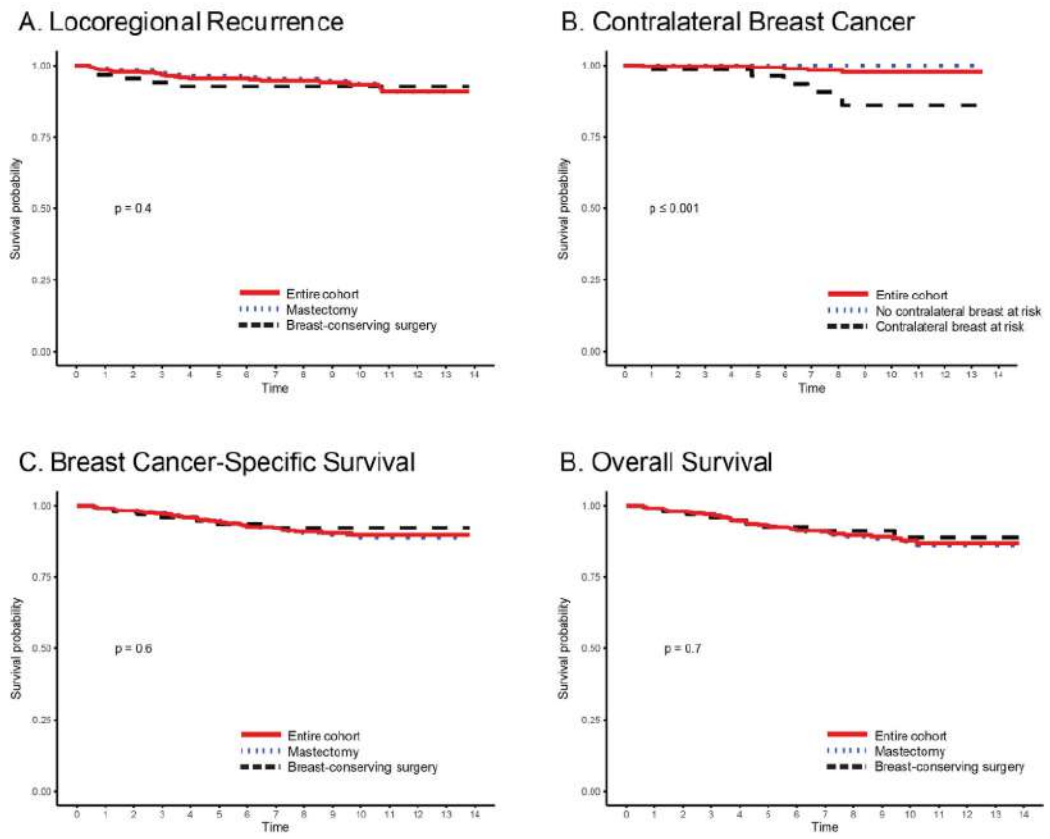


Figure 2. Unadjusted overall survival curves for BRCA1/2-associated breast cancer patients (including patients who deceased or had distant metastases within 2 years after primary breast cancer (PBC) diagnosis) opting for contralateral risk-reducing mastectomy (CRRM) versus not opting for risk-reducing mastectomy (Surveillance), using the Simon and Makuch method—which takes into account the change in an individual's covariate status over time—with years after PBC diagnosis as the time variable.

Greatest benefit in <40 & low risk/favorable features

Heemskerk-Gerritsen, Int J Cancer, 2015

DOES CRRM IMPROVE SURVIVAL?



Shubeck et al, Ann of Surg Oncol, 2022

What's happening in the clinic?

Table 1. Characteristics of the Study Population

Characteristic	Gene with variant, No. (%) of participants						P value
	All (N = 684)	*BRCA1* (n = 235)	*BRCA2* (n = 217)	*PALB2* (n = 121)	*ATM* (n = 50)	*CHEK2* (n = 61)	
Age at first breast cancer diagnosis, mean (range), y	53 (23-83)	50 (23-74)	54 (27-82)	54 (23-83)	58 (36-76)	57 (28-77)	NA
Race and ethnicity[a]							
Asian	4 (1)	1 (0)	1 (1)	2 (2)	0	0	.47
Black	32 (5)	16 (7)	9 (4)	6 (5)	1 (2)	0	
White	623 (91)	210 (89)	203 (94)	106 (88)	46 (92)	58 (95)	
Other	3 (0)	1 (0)	1 (1)	1 (1)	0	0	
Unknown	22 (3)	7 (3)	3 (1)	6 (5)	3 (6)	3 (5)	
First breast cancer surgery							
Lumpectomy	203/524 (39)	72/182 (40)	60/167 (36)	37/91 (41)	10/31 (32)	24/53 (45)	.73
Mastectomy	90/524 (17)	33/182 (18)	34/167 (20)	13/91 (14)	4/31 (13)	6/53 (11)	
Bilateral mastectomy	231/524 (44)	77/182 (42)	73/167 (44)	41/91 (45)	17/31 (55)	23/53 (43)	
Data missing	160/684 (23)	53/235 (23)	50/217 (23)	30/121 (25)	19/50 (38)	8/61 (13)	
Received radiotherapy	260 (38)	95 (40)	79 (36)	48 (40)	14 (28)	24 (39)	.60
Relatives with breast cancer[b]							
No family history	122 (18)	39 (17)	32 (15)	27 (22)	9 (18)	15 (25)	.46
First degree	321 (47)	105 (45)	114 (53)	52 (43)	26 (52)	24 (39)	
Second degree	189 (28)	69 (29)	58 (27)	35 (29)	12 (24)	15 (25)	
Third degree	52 (8)	22 (9)	13 (6)	7 (6)	3 (6)	7 (11)	

Table 2. Multivariate Logistic Regression for Bilateral Mastectomy

Variable	OR (95% CI)	
	Unadjusted	Adjusted
Age at first breast cancer diagnosis, y		
<50	2.97 (2.03-4.35)	2.21 (1.44-3.40)
≥50	1 [Reference]	1 [Reference]
Timing of genetic testing		
Before surgery	6.65 (4.45-9.92)	5.79 (3.83-8.76)
After surgery	1 [Reference]	1 [Reference]
Family history of breast cancer		
No family history	1 [Reference]	1 [Reference]
First-degree relative	0.89 (0.53-1.48)	1.03 (0.57-1.87)
Second-degree relative	1.05 (0.59-1.84)	0.99 (0.52-1.88)
Third-degree relative	0.58 (0.26-1.28)	0.63 (0.25-1.56)
Gene with variant		
BRCA1 or *BRCA2*	1 [Reference]	1 [Reference]
ATM	1.45 (0.66-3.18)	1.62 (0.66-3.95)
CHEK2	0.97 (0.53-1.78)	1.23 (0.63-2.42)
PALB2	1.03 (0.63-1.67)	1.32 (0.76-2.29)

Abbreviation: OR, odds ratio.

Reid et al, JAMA Oncol, 2022

ESMO DEEP DIVE:
BREAST CANCER

RISK GOES BEYOND CANCER DIAGNOSIS….

Reproductive & Psychosocial issues

Reproductive

- Timing of RRSO
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45
- Fertility preservation
- PGD – pre-implantation genetic diagnosis
- Pregnancy after BC - safe
- Premature menopause – impact on sexual health, bone health, quality of life

Psychological

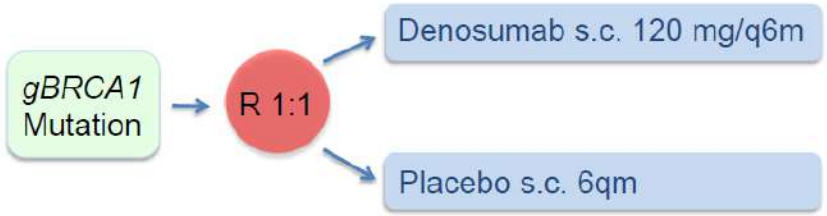
- Knowledge of BRCA1/2 status may arrive at a time of great distress
- Multitude of reproductive & therapeutic /risk reducing decision
- Risk reducing measures are often an assault on self-image, “womanhood”
- Far reaching implications for family planning and for extended family

RRSO = risk reducing salpingo-oophorectomy

Lambertini, JAMA, 2024

FUTURE DIRECTIONS

- Clinical integration of PRS (polygenic risk score) and adaptation for non-Caucasian populations
- Novel risk reducing strategies – BRCA-P study (NCT04711109)– targeting of RANK/RANKL pathway with denosumab in unaffected *BRCA1* carriers who have not undergone BRRM



- Machine learning algorithms and breast imaging interpretation
- Liquid biopsies

SUMMARY

- Risk is a continuum – it varies by gene, by specific variant, by population
- Screening and risk-reduction for individuals with a HBOC syndrome is complex and should be tailored based on risk, family history and patient preference
- In affected carriers choices on ongoing surveillance and risk-reduction must be tailored to stage, natural history of disease and prognosis
- Multi-disciplinary care is critical
- Further research is needed about the management of individuals with HBOC syndromes, particularly those with moderate risk pathogenic variants
- Over-aggressive and non-evidence based screening and risk reducing measures can cause harm
  - *"primum non nocere"*

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

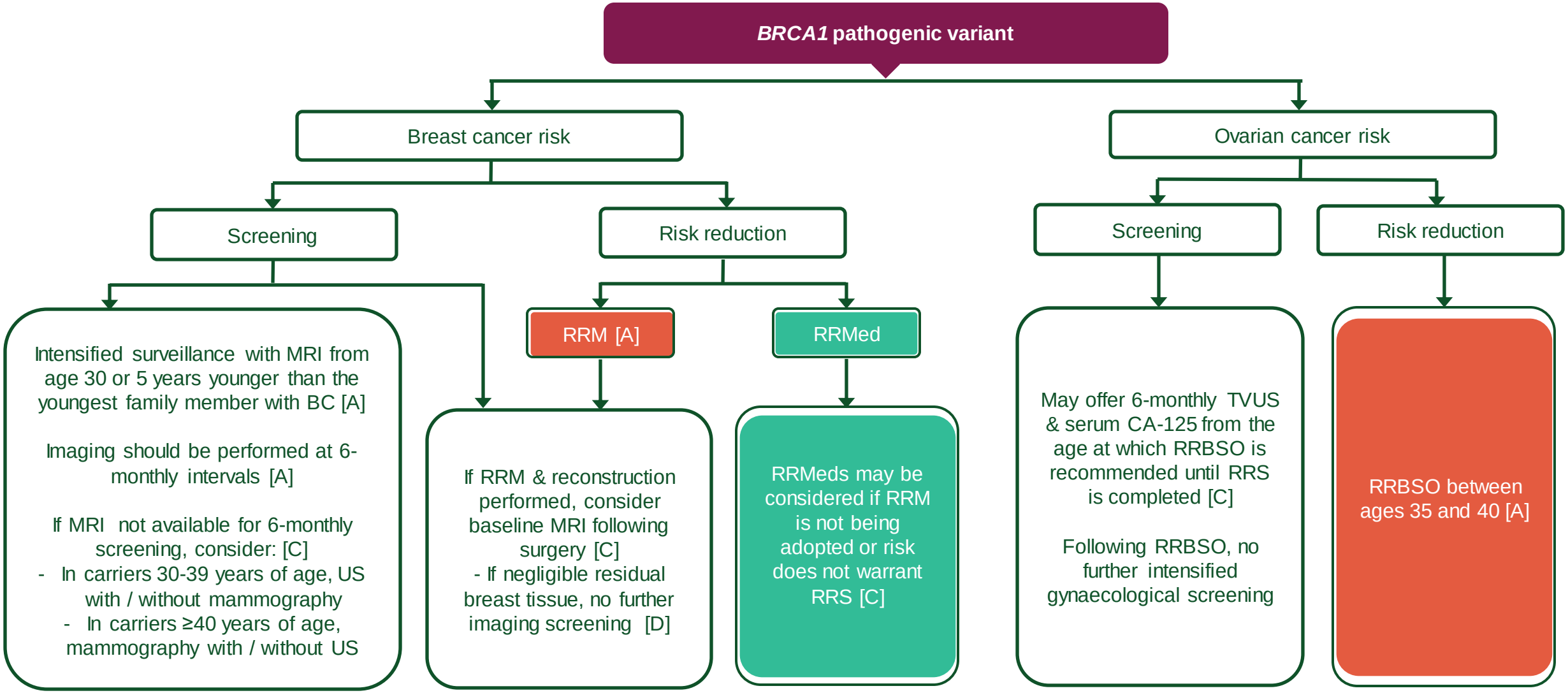
SPECIAL ARTICLE

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

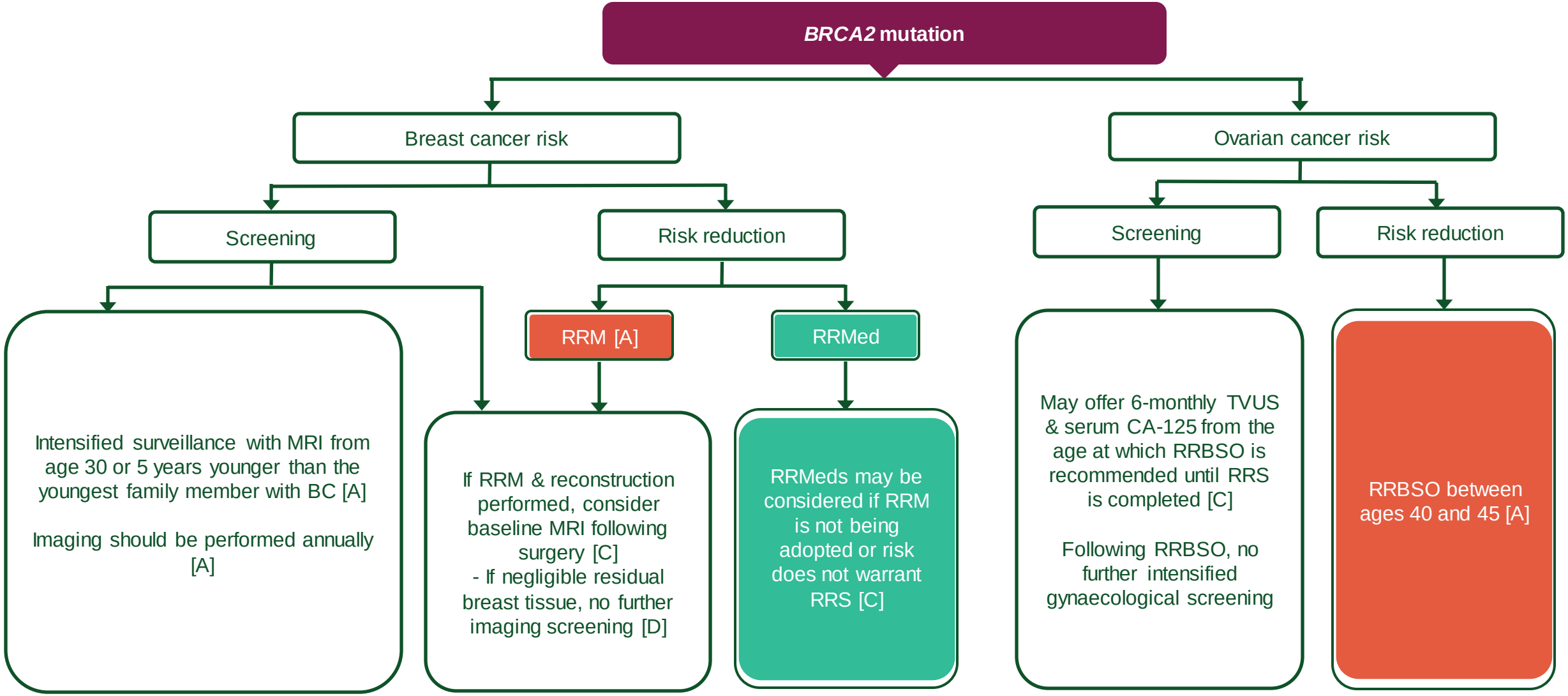
C. Sessa[1], J. Balmaña[2], S. L. Bober[3], M. J. Cardoso[4], N. Colombo[5,6], G. Curigliano[7,8], S. M. Domchek[9], D. G. Evans[10,11], D. Fischerova[12], N. Harbeck[13], C. Kuhl[14], B. Lemley[15,16], E. Levy-Lahad[17], M. Lambertini[18,19], J. A. Ledermann[20], S. Loibl[21], K.-A. Phillips[22] & S.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

[1]Medical Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; [2]Medical Oncology Hospital Vall d'Hebron and Hereditary Cancer Genetics Group, Vall d'Hebron Institut of Oncology, Barcelona, Spain; [3]Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute/Harvard Medical School, Boston, USA; [4]Champalimaud Foundation, Breast Unit and Faculdade de Medicina, Lisbon, Portugal; [5]Department of Gynecologic Oncology, Istituto Europeo di Oncologia e IRCCS, Milan; [6]Department of Medicine and Surgery, University of Milano-Bicocca, Milan; [7]Early Drug Development for Innovative Therapies Division, Istituto Europeo di Oncologia, IRCCS, Milan; [8]Department of Oncology and Hemato-Oncology, University of Milano, Milan, Italy; [9]Basser Center for BRCA, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [10]Manchester Centre for Genomic Medicine, Division of Evolution Infection and Genomic Sciences, University of Manchester, MAHSC, Manchester; [11]Manchester Centre for Genomic Medicine, MAHSC, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [12]Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic; [13]Breast Center, Department of Obstetrics & Gynecology and Comprehensive Cancer Center Munich, LMU University Hospital, Munich; [14]Department of Diagnostic and Interventional Radiology, University Hospital Aachen, University Hospital Aachen (UKA), RWTH Aachen, Germany; [15]KIU — Patient Organisation for Women with Gynaecological Cancer, Copenhagen, Denmark; [16]Clinical Trials Project, ESGO ENGAGe, Prague, Czech Republic; [17]Medical Genetics Institute, Shaare Zedek Medical Center; Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel; [18]Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova; [19]Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [20]Department of Oncology, UCL Cancer Institute, University College London and UCL Hospitals, London, UK; [21]GBG Forschungs GmbH, Neu-Isenburg, Germany; [22]Department of Medical Oncology, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia; [23]Sharett Institute of Oncology Department, Hadassah University Hospital & Faculty of Medicine Hebrew University, Jerusalem, Israel

Summary - Screening & Risk Reduction – *BRCA1*



Summary - Screening & Risk Reduction – *BRCA2*



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