Breast Cancer Screening and Prevention

Zia Poonja MD FRCPC

Disclosures

	Nature of relationship(s) (past 2 years)	**Name of for-profit or not-for-profit organization(s)**	**Description of relationship(s)**
A	Any direct financial payments including receipt of honoraria	AstraZeneca, Merck, Takeda	Honoraria for CME speaking events
B	Membership on advisory boards or speakers' bureaus	Novartis, Takeda, Eli Lilly, Seagen	Honoraria for attending consultancy meetings

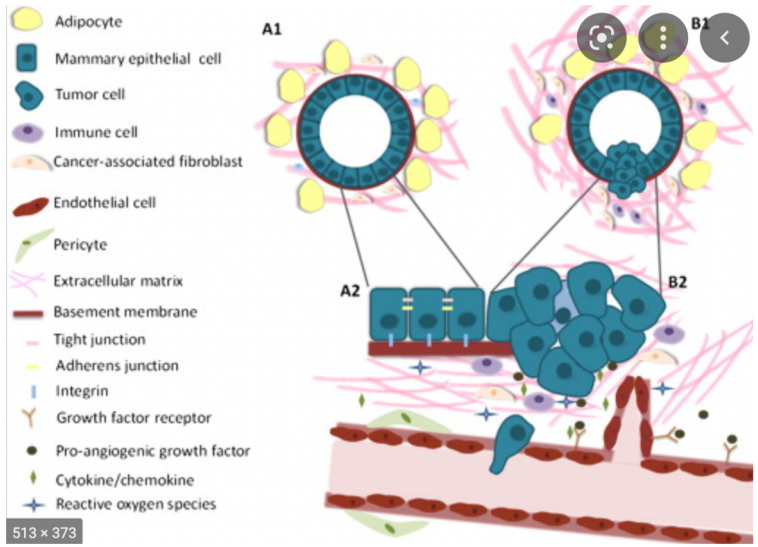
Objectives

By the end of this session, participants will be able to:

1) Briefly describe the pathogenesis of breast cancers and their biology;
2) Review screening recommendations; and
3) Identify strategies to prevent breast cancers

Pathogenesis

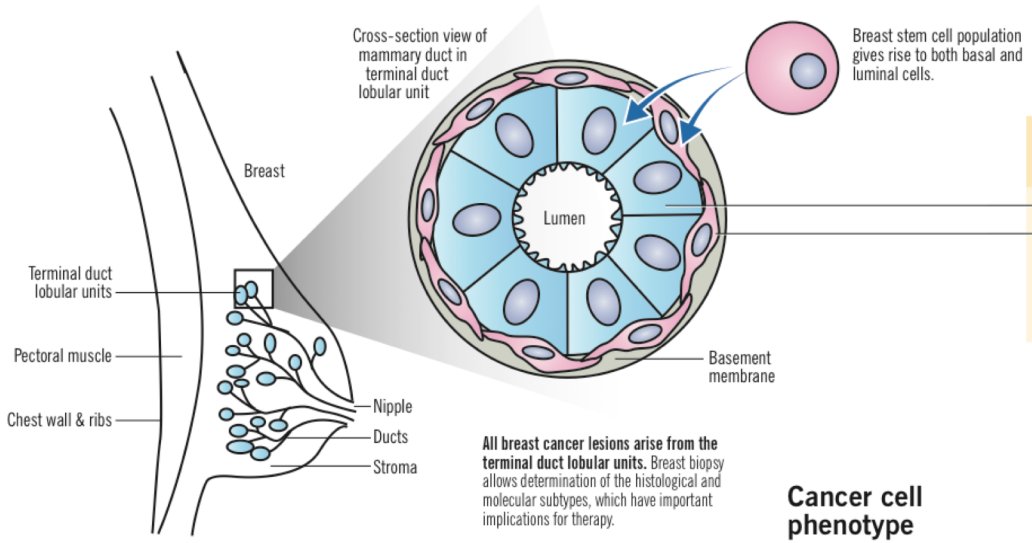
- Most breast cancers are epithelial tumors that develop from cells lining ducts or lobules; less common are nonepithelial cancers of the supporting stroma (eg, angiosarcoma, primary stromal sarcomas, phyllodes tumor).



Mafalda Videira, Rita Leones Reis, Maria Alexandra Brito, Deconstructing breast cancer cell biology and the mechanisms of multidrug resistance, Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, Volume 1846, Issue 2, 2014, Pages 312-325,ISSN 0304-419X,https://doi.org/10.1016/j.bbcan.2014.07.011.

Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo



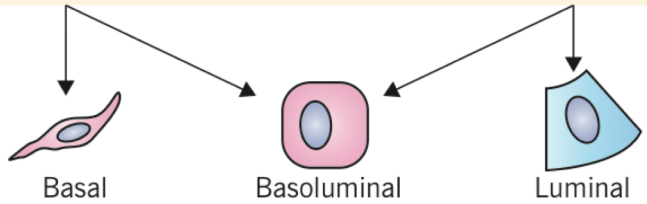
All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells
- Contractile cells for milk ejection
- *Estrogen receptor* –
- Progesterone receptor –

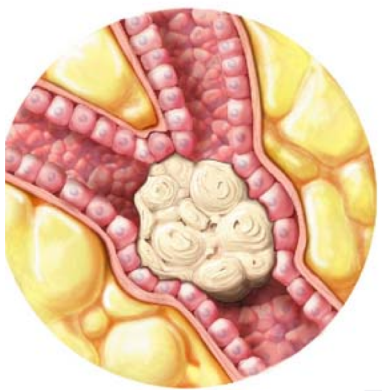
Luminal or epithelial cells
- Respond to hormonal stimulation for milk production
- *Estrogen receptor* +
- Progesterone receptor +/–

Cancer cell phenotype

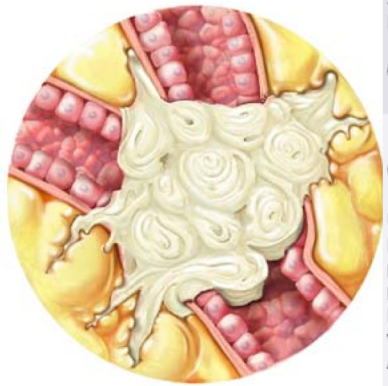


Histological subtypes	Ductal	Lobular
Preinvasive cancer 25%	Ductal carcinoma in situ (DCIS) 80%	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
		Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Ductal carcinoma in situ



Infiltrating (invasive) ductal carcinoma



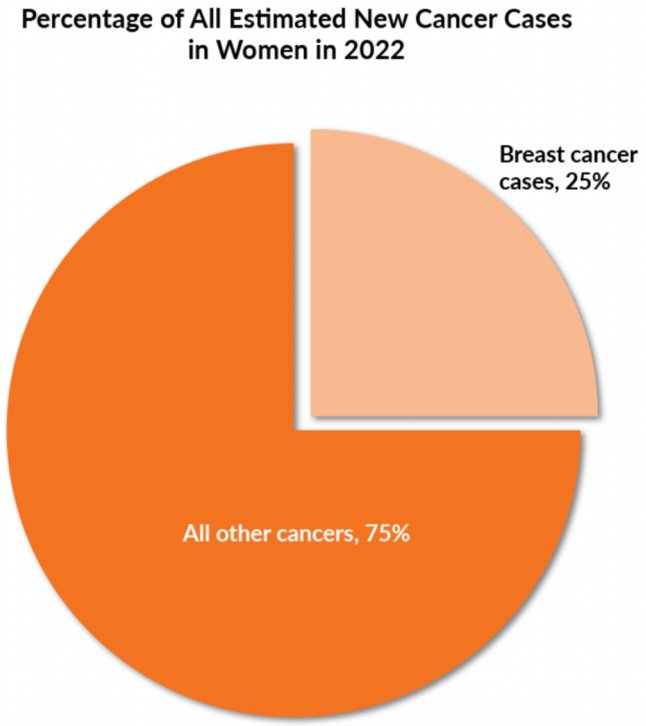
Molecular subtypes	Triple negative ER–, PR–, HER2–	HER2+	Luminal B	Luminal A
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade Level of cell differentiation	High (grade III)			Low (grade I)
Prognosis Correlates to histologic grade	Poor			Good
Response to medical therapy	Chemotherapy	Trastuzumab		Endocrine

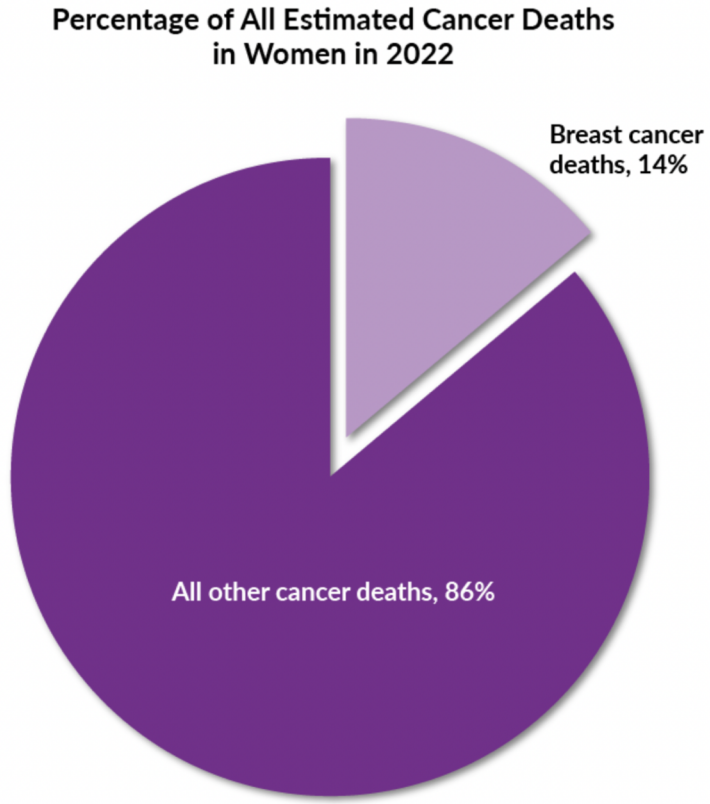
Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.
Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins 8E

- The incidence rate of breast cancer among females increased to the mid-1990s and has oscillated throughout the last 2 decades.
- Breast cancer will affect 1 in 8 women (by age 85)
- Leading cause of cancer related disease burden for women





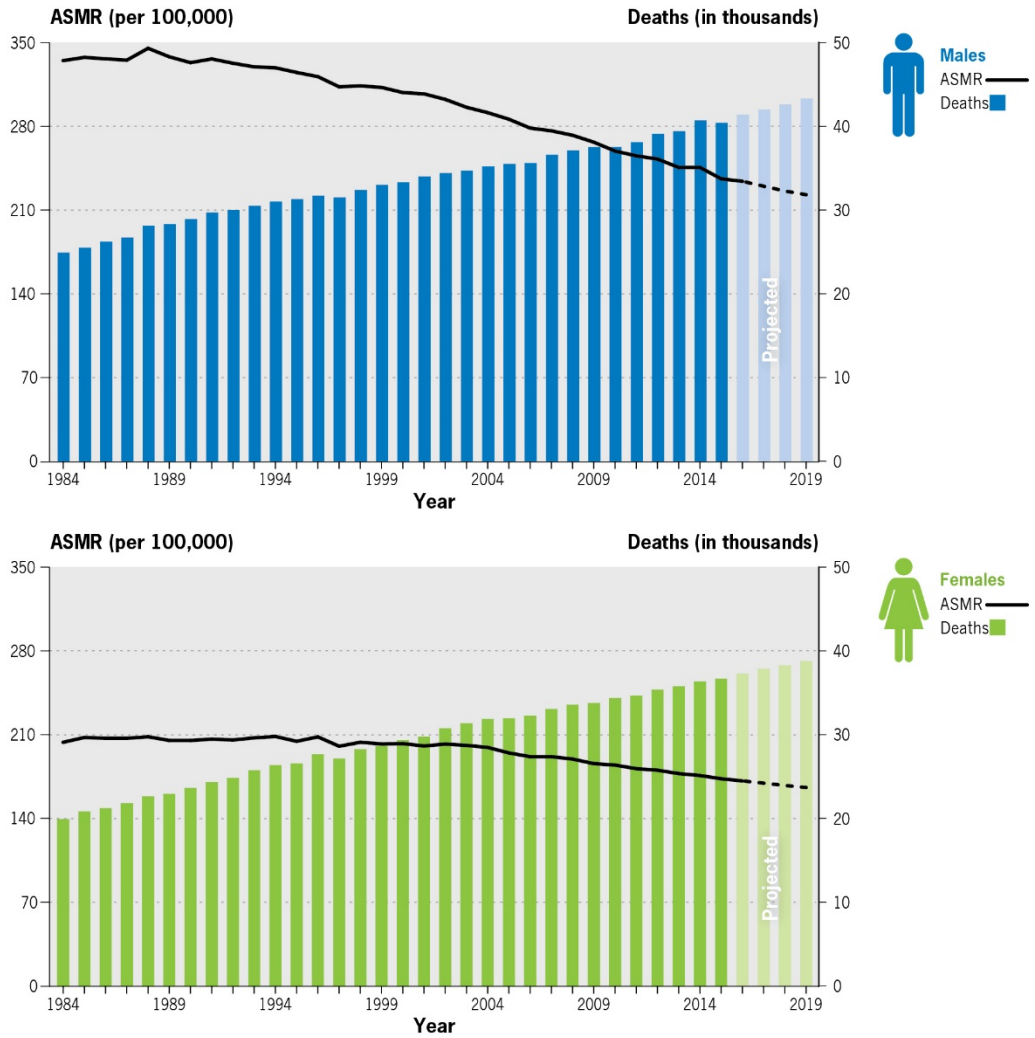
CMAJ 2022 May 2;194:E601-7. doi: 10.1503/cmaj.212097

Treatment

- Over the past 5 years treatments for metastatic breast cancer have dramatically changed
- Advances in our understanding of what kinds of treatments benefit women has radically changed
- Significant de-escalations in treatment with the use of genetic tool to sequence breast cancers

Mortality rates for cancer are decreasing

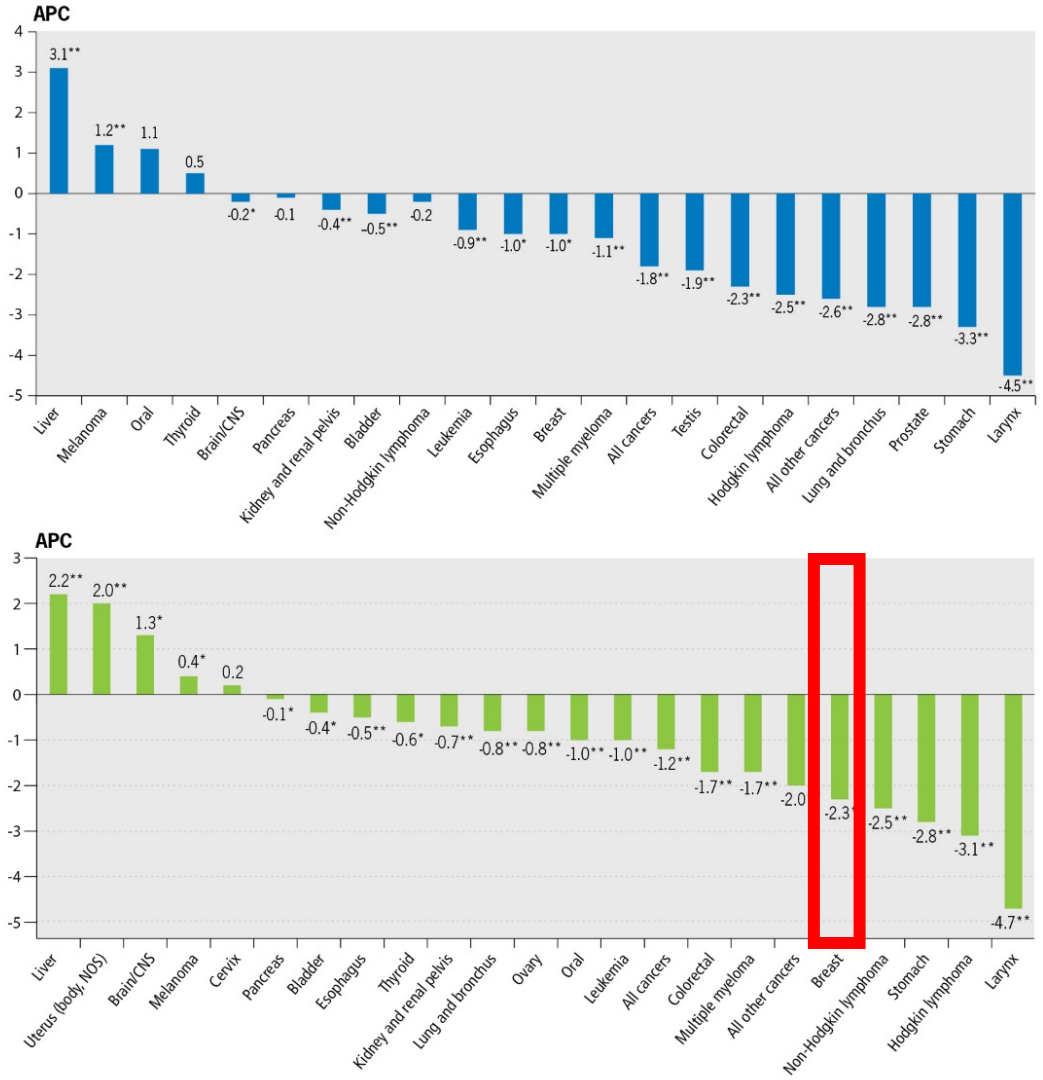
FIGURE 2.6 Deaths and age-standardized mortality rates (ASMR) for all cancers, Canada, 1984–2019



Analysis by: Centre for Surveillance and Applied Research, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death Database at Statistics Canada

Note: Rates are age-standardized to the 2011 Canadian population. Actual data were available to 2015 and projected thereafter.

FIGURE 2.7 Most recent annual percent change (APC)† in age-standardized mortality rates (ASMR), by sex, Canada, 1984–2015



-2.3% annual percent change in age standardized mortality

CNS=central nervous system; NOS=not otherwise specified

* APC differs significantly from 0, p<0.05

** APC differs significantly from 0, p<0.001

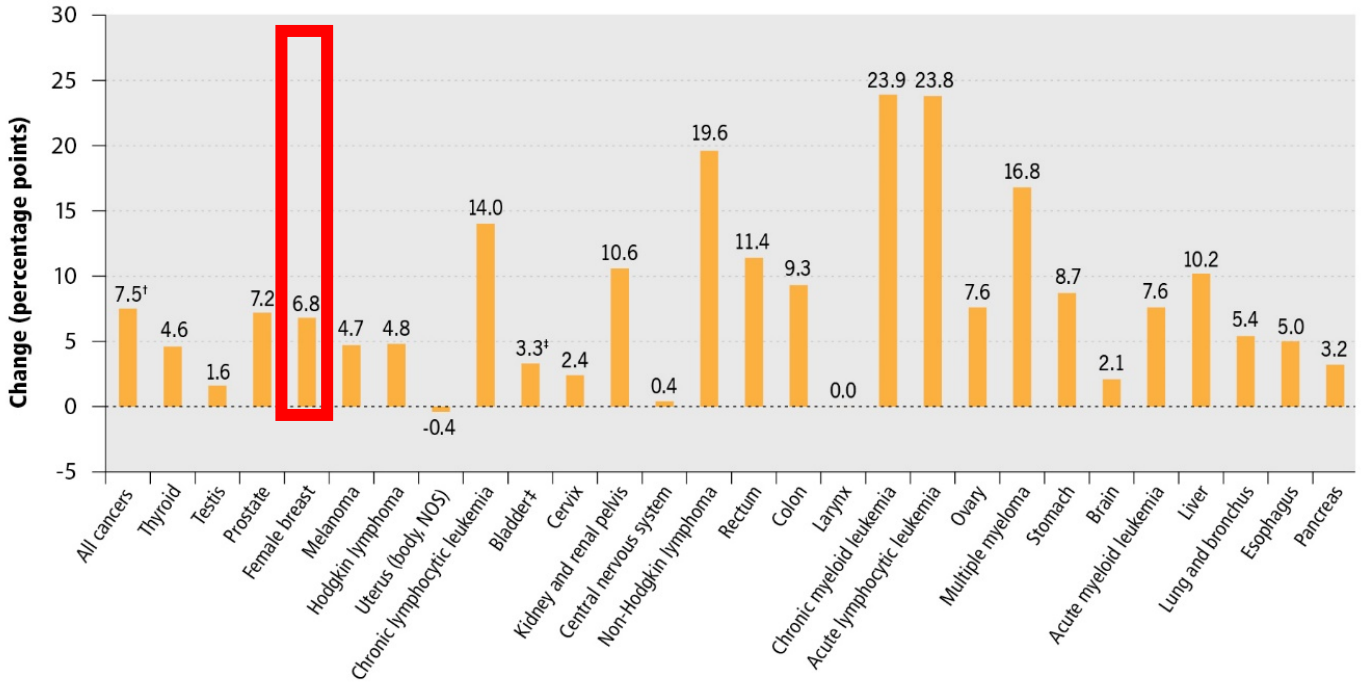
† The APC was calculated using the Joinpoint Regression Program using rates from 1984–2015. If one or more significant change in the trend of rates was detected, the APC reflects the trend from the most recent significant change (reference year) to 2015. If no significant change in trend was detected, the APC reflects the trend in rates over the entire period (1984–2015). The reference year for each cancer is in Table 2.6. For further details, see *Appendix II: Data sources and methods*.

Note: The range of scales differs widely between the figures.

Analysis by: Centre for Surveillance and Applied Research, Public Health Agency of Canada

Data source: Canadian Vital Statistics Death Database at Statistics Canada

FIGURE 3.2 Predicted change in five-year age-standardized net survival between 1992–1994 and 2012–2014 for selected cancers, ages 15–99, Canada (excluding Quebec*)



NOS=not otherwise specified

* Does not include Quebec because cases diagnosed in Quebec from 2011 onward have not been submitted to the Canadian Cancer Registry.

† Estimates for all cancers combined were calculated as a weighted average of estimates for individual cancers. For further details, see *Appendix II: Data sources and methods*.

‡ Does not include *in situ* cases for Ontario diagnosed prior to 2010 because they were not submitted to the Canadian Cancer Registry.

Note: For each cancer in turn, the age distribution of persons recorded as being diagnosed with the given cancer in Canada, excluding Quebec, from 2010 to 2014 was used as the standard (see *Appendix II: Data sources and methods*). The complete definition of the specific cancers listed here can be found in Table A1.

Analysis by: Centre for Population Health Data, Statistics Canada

Data sources: Canadian Cancer Registry death linked file (1992–2014) and life tables at Statistics Canada. Partially adapted from Table 2 in Ellison LF. Progress in net cancer survival in Canada over 20 years. Health Reports 2018; 29(9):10–8.

6.8% improvement in survival in 2012-2014 compared to 1992-1994

Earlier intervention is the key to success

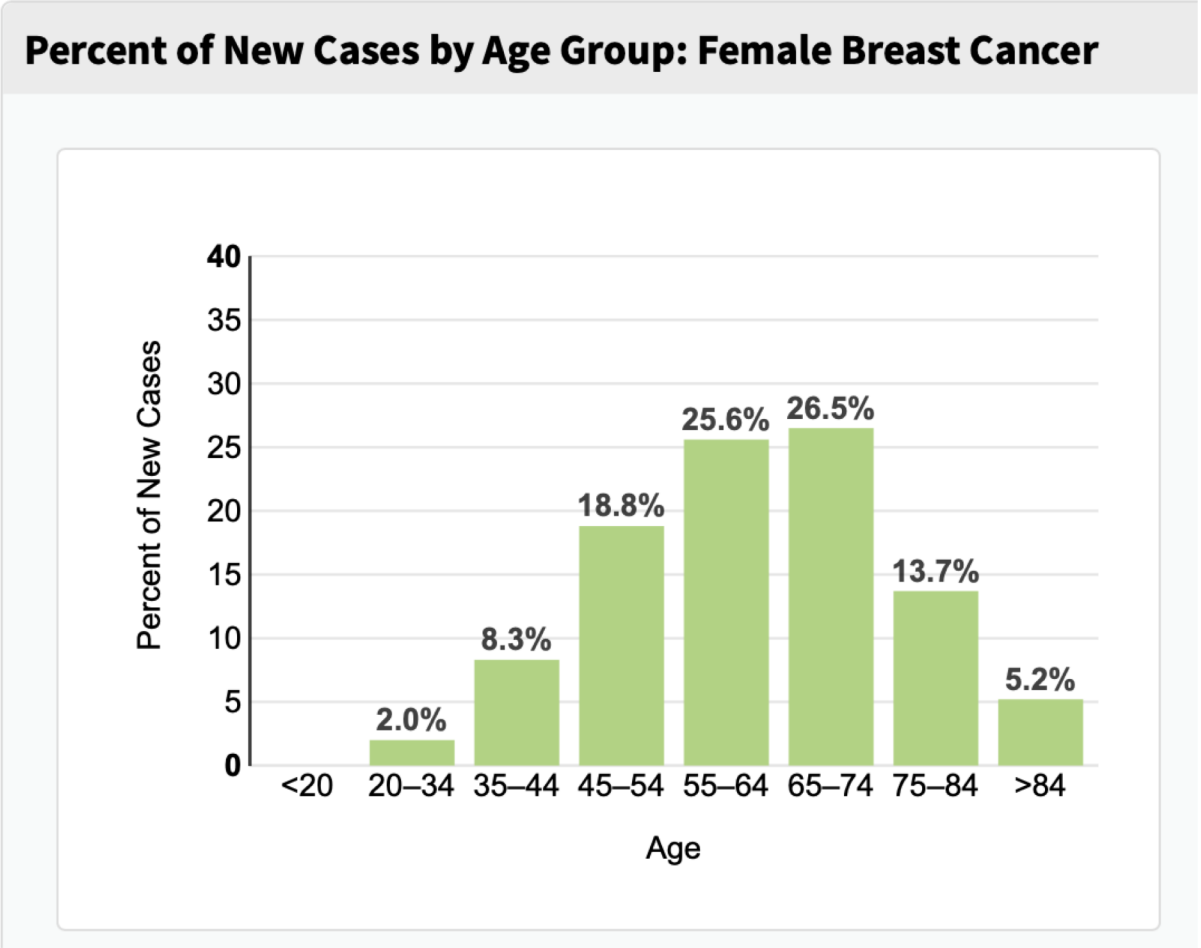
Breast cancer survival	
Stage	5-year relative survival
0	100%
1	100%
2	93%
3	72%
4	22%

https://cancer.ca/en/cancer-information/cancer-types/breast/prognosis-and-survival/survival-statistics

Screening → Precision screening

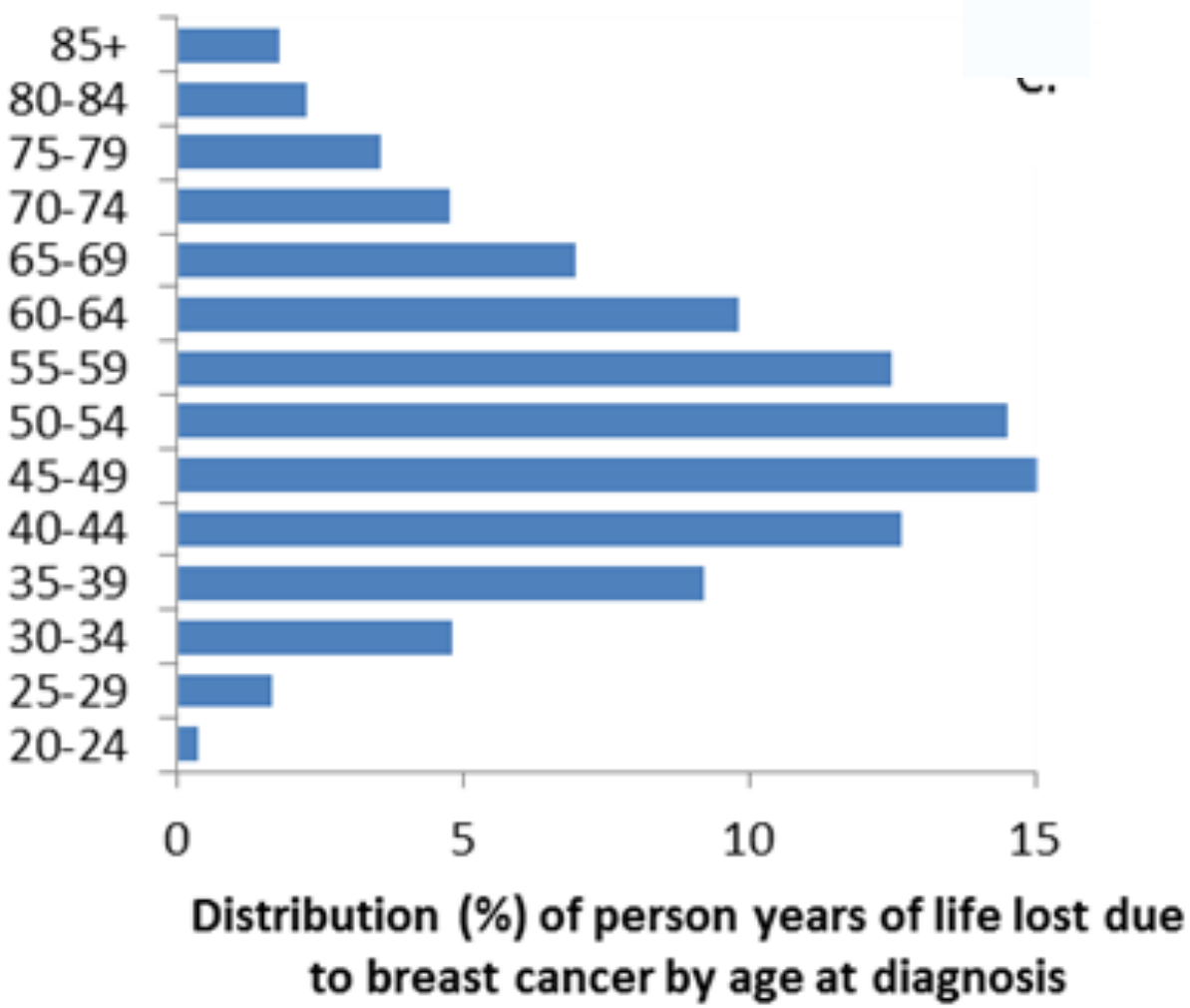
Breast cancer risk increases with age

CANCERS PER 1000 SCREENS	
AGE	CANCERS DETECTED
40-49	2 out of 1000
50-59	4 out of 1000
60-69	6 out of 1000



https://seer.cancer.gov/statfacts/html/breast.html

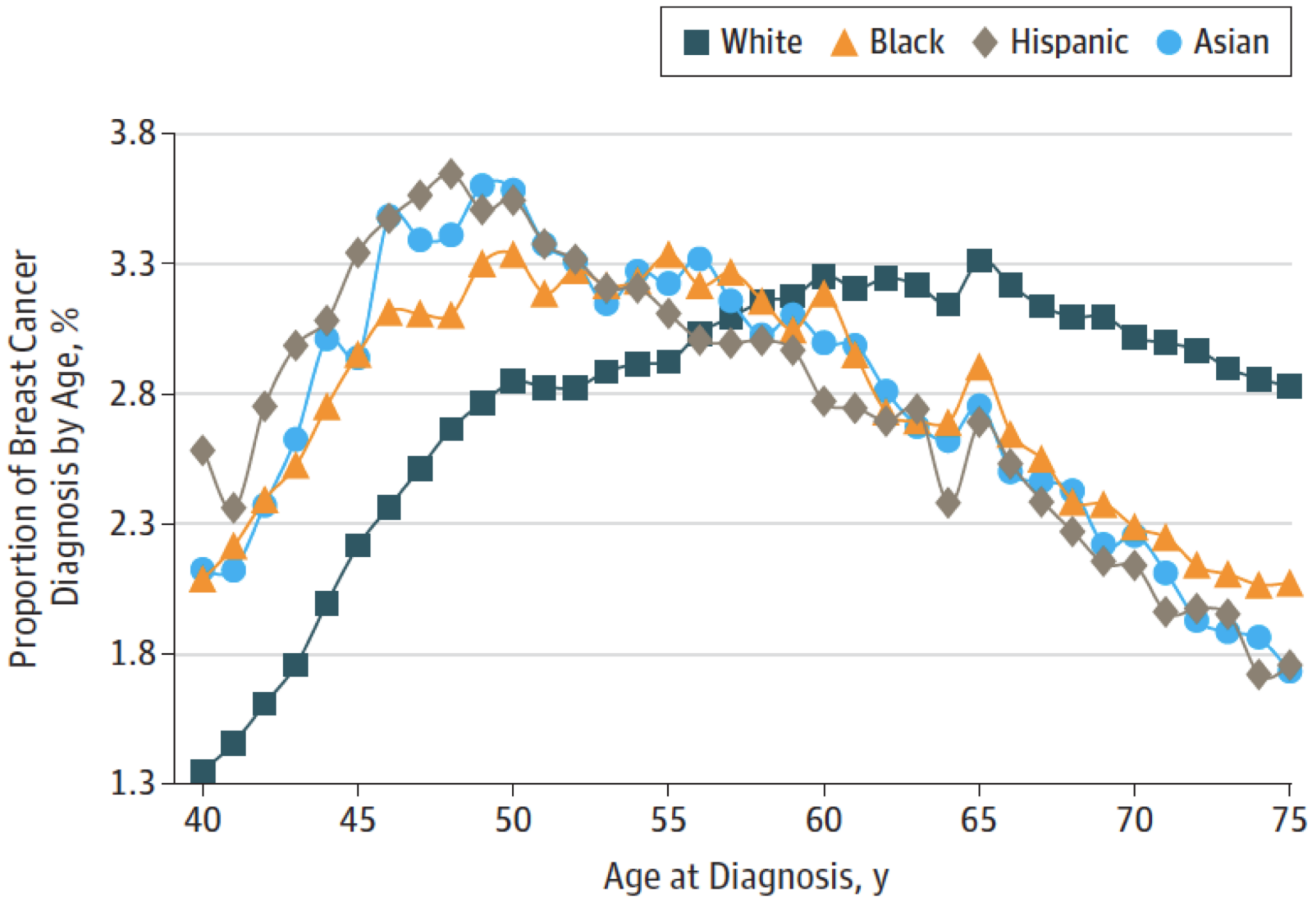
Years of Life Lost to Breast Cancer



Oeffinger KC, et al. JAMA. 2015;314:1599-614

Stapleton SM et al JAMA Surg 2018;153:594-595

Figure 1. Distribution of Age at Diagnosis for Women With Breast Cancer



Courtesy of Drs. Wendie Berg and Paula Gordon

Mammograms

- Trials have shown a 25 per cent reduction in deaths from breast cancer among women who are screened regularly.

Proof that Screening Saves Lives

11 Randomized Trials

• NYHIP		1963
• Malmö 1		1976
• Malmö 2		1978
• Kopparberg		1976
• Östergötland		1978
• Edinburgh		1978
• CNBSS 1		1980
• CNBSS 2		1980
• Stockholm		1981
• Göteberg		1982
• Finland		1987

And Dozens Of Systematic Reviews And Meta-analyses

Courtesy Drs. Jean Seely and Paula Gordon

Trial	# of women	Age range	Follow-up interval (years)	RR for breast CA mortality
New York	60 686	40-64	18	0.78
Malmö I	42 283	45-70	19.2	0.81
Malmö II	17 793	43-49	9.1	0.65
Kopparberg, Two-county	56 448	40-74	20	0.59
Östergötland, Two-county	76 617	40-74	17.4	0.89
Edinburgh	44 268	45-64	12.6	0.78
Canada CNBSS I	50 430	40-49	13	1.06
Canada CNBSS II	39 405	50-59	13	1.02
Stockholm	60 117	40-64	14.9	0.90
Göteborg	51 611	39-59	13.3	0.78
Finland	158 755	50-64	4.4	0.76

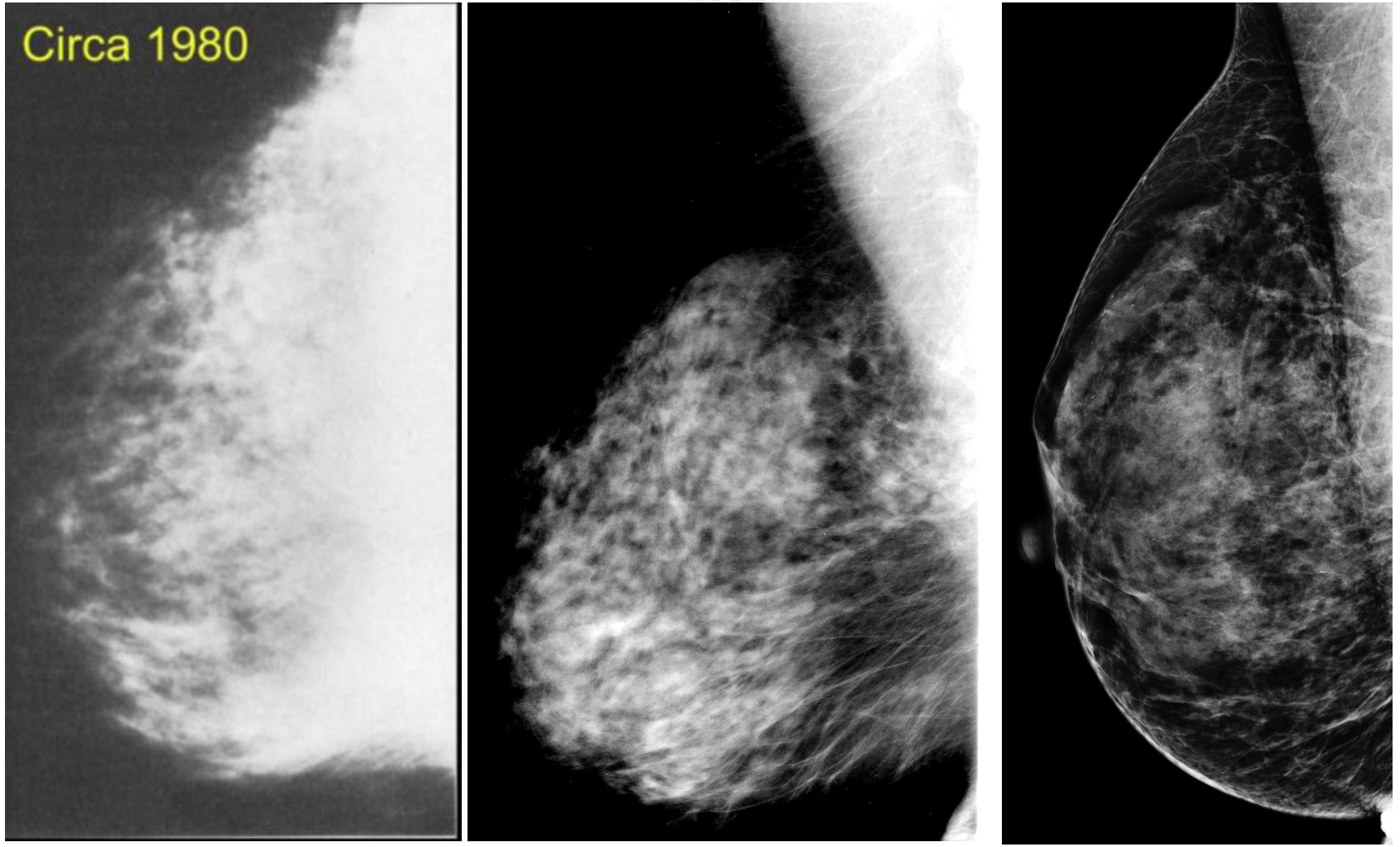
Courtesy Drs. Jean Seely and Paula Gordon

CNBSS

Sweden

1981

2021



Courtesy Dr. Paula Gordon

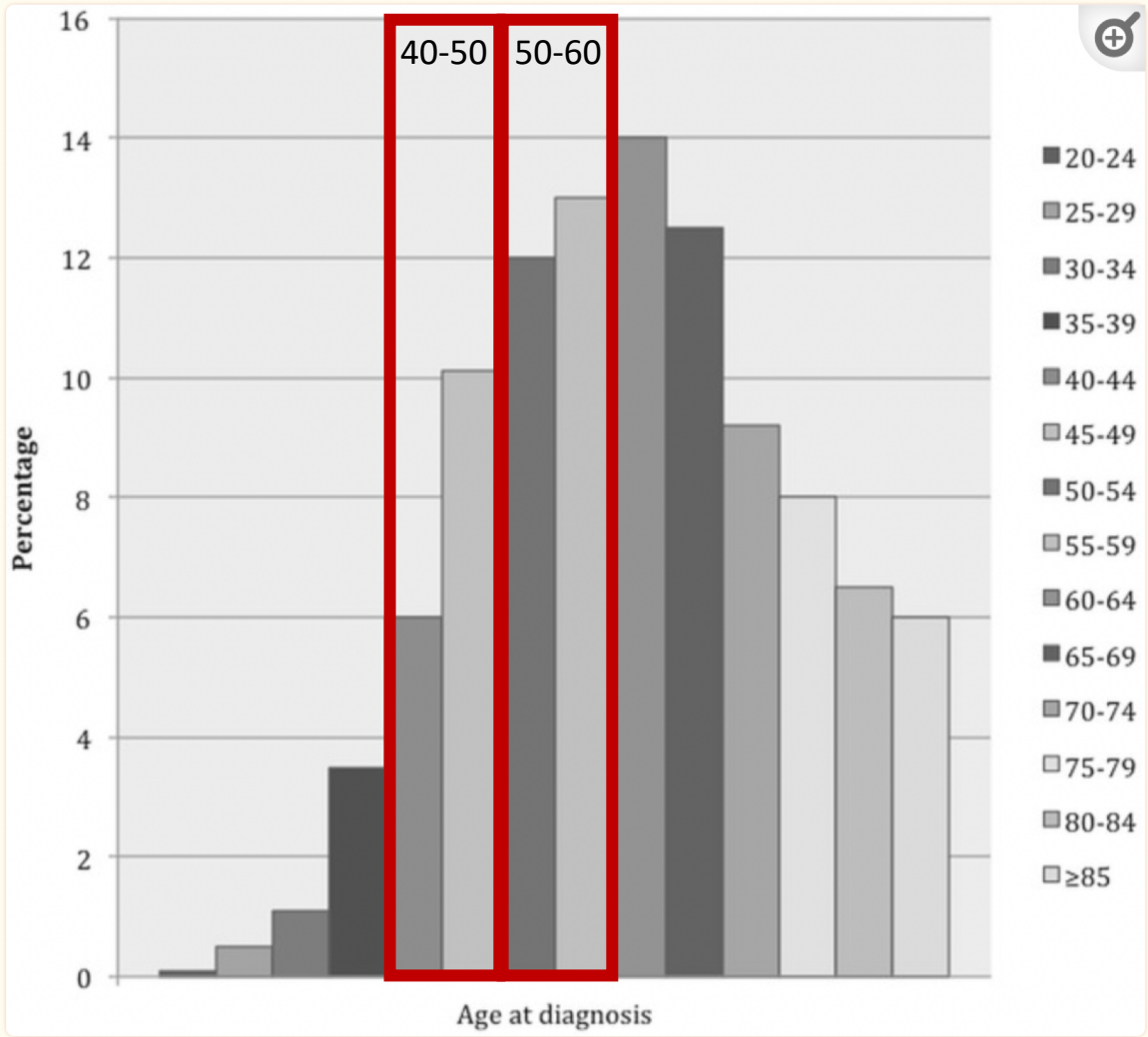


FIGURE 1

Breast cancer (BCa) burden by age at diagnosis, 2007–2011. (A) Distribution of invasive female BCa cases (n = 292,369) by age at diagnosis. (B) Distribution of BCa deaths (n = 16,789, patients followed for up to 20 years) by age at diagnosis. (C) Distribution of person–years of life lost to BCa (n = 326,560, patients followed for up to 20 years) by age at diagnosis. Source: Oeffinger *et al.,* 2015[10].

Best available current evidence, screening mammography should be recommended every 1–2 years for women 40–74 years of age at average risk

Seely JM, Alhassan T. Screening for breast cancer in 2018-what should we be doing today?. *Curr Oncol*. 2018;25(Suppl 1):S115-S124. doi:10.3747/co.25.3770

Table 1

Breast cancer deaths averted, mortality reduction, life-years (LY) saved, screening examinations and women needed to be screened per death averted, and women needed to be screened per LY, compared with No Screening, by screening strategy,

Screening strategy	Breast cancer deaths averted per 1,000 women alive at age 40	Mortality reduction (%) with 15 years follow-up	LY gained per 1,000 women alive at age 40	Maximum screening examinations per woman	Screening examinations per death averted	Women screened per death averted	Women screened per LY gained
Annual 40 to 69	9.1	50.2	201.1	30	2,984	99	4.5
Annual 40 to 74	10.1	53.4	213.5	35	3,023	86	4.1
Annual 50 to 69	7.4	45.5	148.0	20	2,360	118	5.9
Annual 50 to 74	8.4	49.2	160.9	25	2,484	99	5.2
Biennial 40 to 74	7.3	38.5	149.8	18	2,165	138	6.7
Biennial 50 to 69	5.2	32.3	105.2	10	1,696	170	8.4
Biennial 50 to 74	6.1	35.9	116.3	13	1,783	137	7.2
Triennial 50 to 69	4.0	24.6	80.0	7	1,557	222	11.1
Triennial 50 to 74	4.8	27.9	89.2	9	1,589	177	9.4
Annual 40 to 49, Biennial 50 to 69	7.0	38.7	158.2	20	2,651	133	5.9
Annual 40 to 49, Biennial 50 to 74	7.9	42.0	170.3	22	2,593	118	5.5

Yaffe MJ, Mittmann N, Lee P, et al. Clinical outcomes of modelling mammography screening strategies. *Health Rep*. 2015;26(12):9-15.

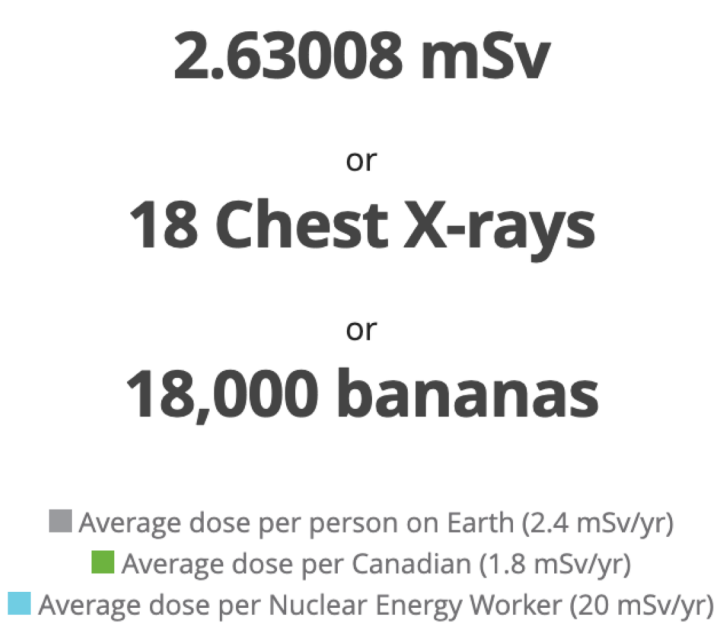
Table. Screening Mammography Program of BC guidelines for primary care providers.

Physician Protocol for Screening Mammograms

RISK	POLICY
Average risk **Ages 40-49**	Health care providers are encouraged to discuss the benefits and limitations of screening mammography with asymptomatic women in this age group. If screening mammography is chosen, it is available every **two years**. Patients will be recalled every two years.
Average risk **Ages 50-74**	Routine screening mammograms are recommended every **two years** for asymptomatic women at average risk of developing breast cancer. Patients will be recalled every two years. A health care provider's referral is not required.
Average risk **Ages 75+**	Health care providers are encouraged to discuss the benefits and limitations of screening mammography with asymptomatic women in this age group. Health care providers should discuss stopping screening when there are comorbidities associated with a limited life expectancy or physical limitations for mammography that prevent proper positioning. If screening mammography is chosen, it is available every **two to three years**. Patients will not be recalled by the Screening Mammography Program of BC.
Higher than average risk **Ages 40-74 with a first degree relative with breast cancer**	Routine screening mammograms are recommended **every year**. Patients will be recalled every year. A health care provider's referral is not required.
High risk **With a known BRCA1 or BRCA2 mutation or prior chest wall radiation or strong family history of breast cancer**	Age 40-74: please refer to recommendation for "Higher than average risk" women. Under age 40: The Screening Mammography Program accepts women at high risk of developing breast cancer **with a health care provider's referral**, provided they do not have breast implants or an indication for a diagnostic mammogram.

Source: BC Cancer

Radiation



- Radiation is minimal
- Modern-day mammography uses 0.4 millisieverts, or mSv. (A mSv is a measure of radiation dose).
- Perspective = we are normally exposed to 3 mSv of radiation each year just from our natural surroundings.
- The radiation dose used for a screening mammogram of both breasts is about the same amount of radiation a woman would get from her natural surroundings in about 8 weeks.

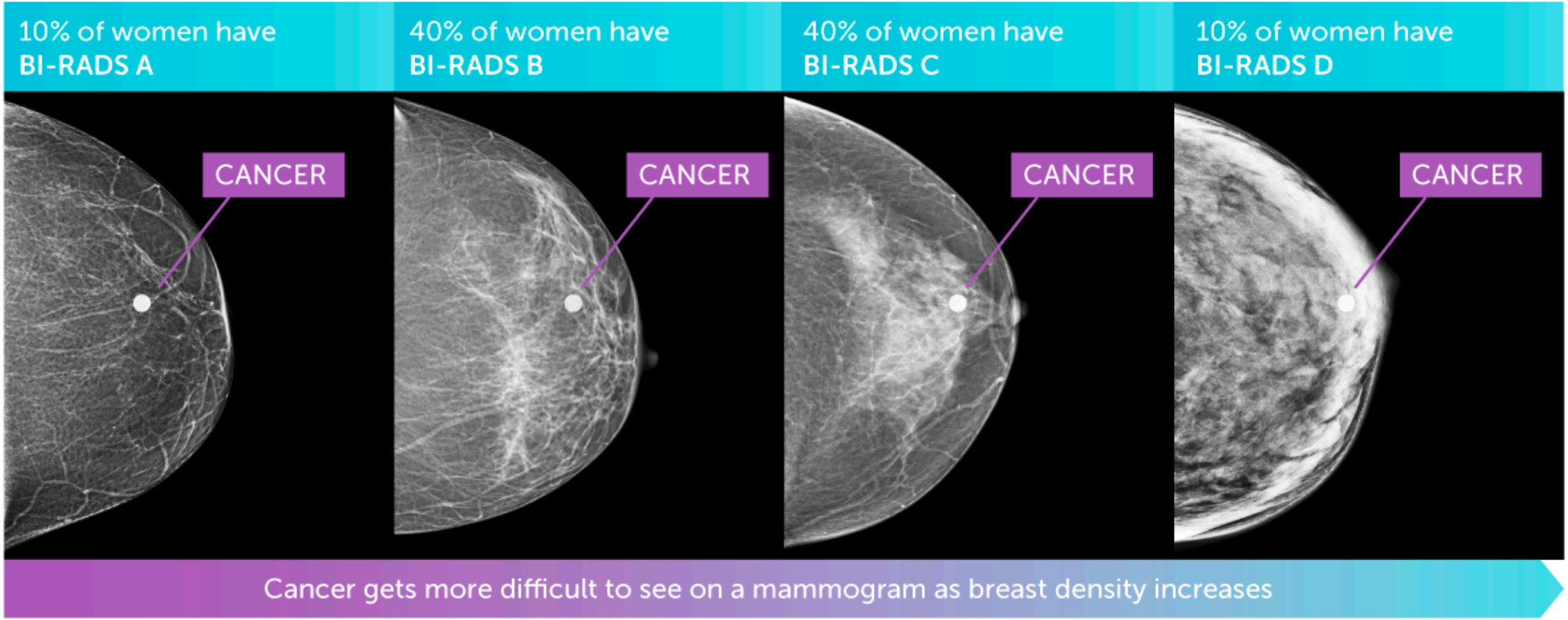
https://fedorukcentre.ca/resources/canadian-radiation-dose-calculator.php

Additional tests

- False positives - 10% false positives that occur in mammography, 8 of 10 are resolved by taking additional views or obtaining ultrasound images, with the remaining 2 being resolved by biopsy. For women who undergo biopsy, only 1 in 3 will be diagnosed with a malignancy.(**over 95% of patients recalled for additional testing do not have cancer**)
- False negatives – mammograms do not detect all cancers, About 25 percent of cancers in women ages 40-49 are not detectable by a screening mammogram, compared with about 10 percent in women older than 50. Location of cancer and breast density plays a role. (80% sensitivity, 63% in very dense breasts)

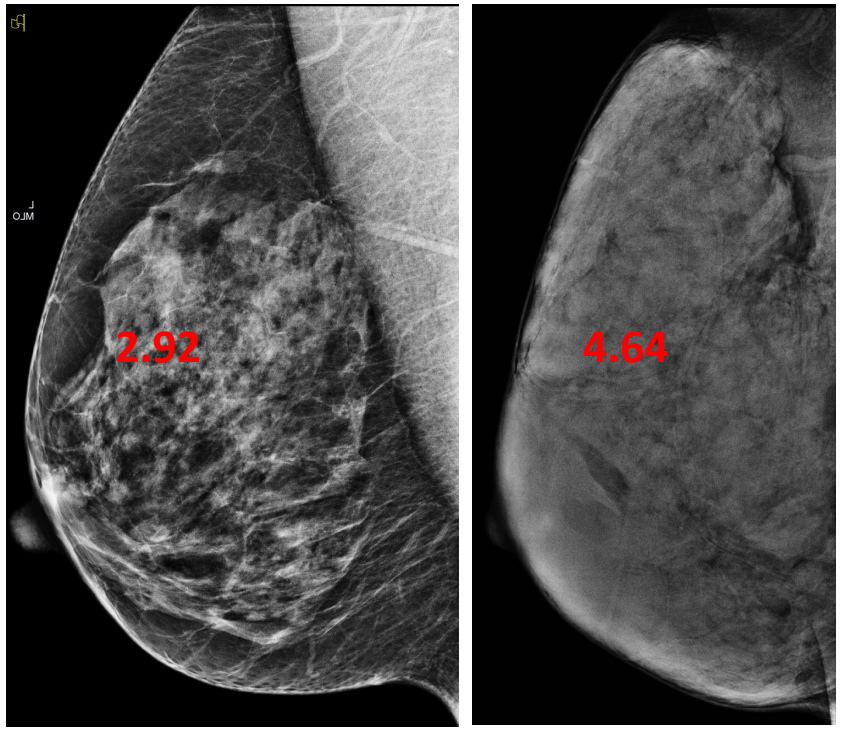
Seely JM, Alhassan T. Screening for breast cancer in 2018-what should we be doing today?. *Curr Oncol*. 2018;25(Suppl 1):S115-S124. doi:10.3747/co.25.3770

Dense Breasts



Breast Density

- Independent risk factor for increased breast cancer risk
- The RR increase is 1.2-6 in women with high mammographic density compared to low mammographic density (1)
- Meta-analysis of 42 studies showed the RR for breast cancer was 2.92 and 4.64 for women with heterogeneously dense or extremely dense breasts compared to fatty breasts (1)



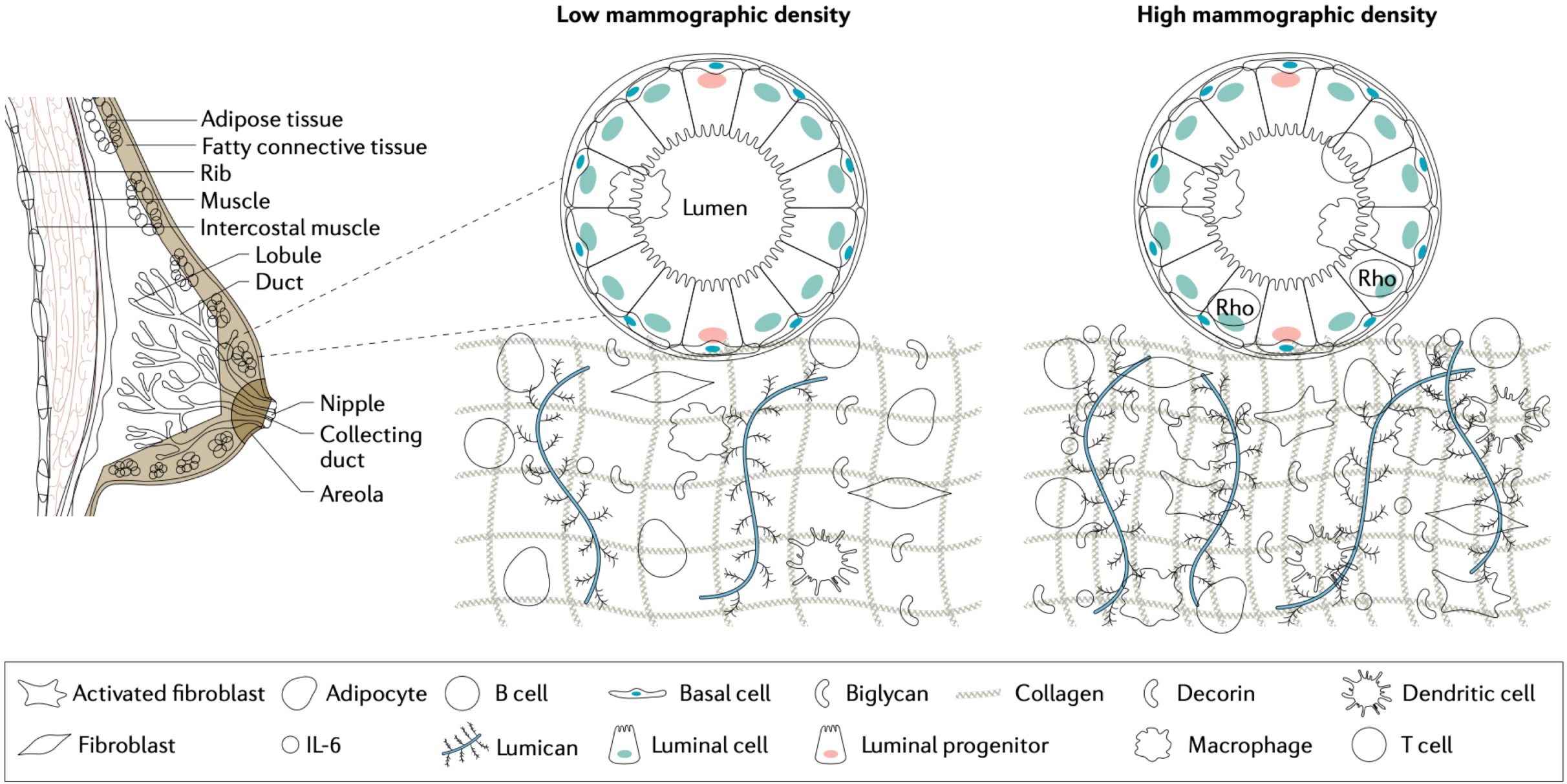
Heterogeneously Dense

Extremely Dense

C

D

(1) McCormack, V. A. & dos Santos Silva, I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* **15**, 1159–1169 (2006).



Britt, K.L., Cuzick, J. & Phillips, KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer* **20,** 417–436 (2020). https://doi.org/10.1038/s41568-020-0266-x

- Pathophysiology underlying dense breast is poorly understood
- Lack of a clear clinical pathway for management of women with dense breasts
- Still benefit from mammograms (lower sensitivity)
- Need for additional imaging (US, MRI) is clear but pathway is not well established

Breast Cancer Screening Effect Across Breast Density Strata: A Case-Control Study

van der Waal et al. Int J Cancer 2017;140:41-4

- Sensitivity better in the fatty than in the dense group (75.7% vs 57.8%).
- Estimated mortality reduction of 13% in women with dense breasts compared to 41% in women with fatty breasts.
- Reduced benefit from mammographic screening is attributed to the masking effect of dense tissue with tumors detected later, when they were larger, in women with dense breasts

Courtesy of Dr. Paula Gordon

Case

- 42F East Asian, BMI 30, Menarche 12, G0P0, premenopausal, took OCP for 5 years. Mother has been diagnosed with breast cancer at 69. Never been for a mammogram.

IBIS Breast Cancer Risk Estimate Results:

Ten Year Risk:
This woman's Risk (at age 42): **3.9%**
Average women (at age 42): **1.9%**

Lifetime Risk:
This woman's Risk (to age 85): **20.8%**
Average woman (to age 85): **10.6%**

This woman's estimated risk for developing breast cancer over the next 10 years is 3.9% compared to a risk of 1.9% for a woman of the same age from the general population. The lifetime risk for developing breast cancer (to age 85) is 20.8% compared to a risk of 10.6% for a woman of the same age from the general population. This calculation also means that this woman's chance of remaining breast-cancer free over the next 10 years is 96.1%.

Case

A) Screening breast program with mammograms every 2 years
B) Screening breast program with mammograms yearly
C) Discuss yearly mammograms - Screening breast program with mammograms every 2 years, plus ordering a mammogram in between
D) Yearly mammograms plus yearly ultrasound
E) Do nothing

- 42F East Asian, BMI 30, Menarche 12, G0P0, premenopausal, took OCP for 5 years. First screening mammogram shows very dense breasts (Cat D)

IBIS Breast Cancer Risk Estimate Results:

Ten Year Risk:
This woman's Risk (at age 42): **3.3%**
Average women (at age 42): **1.9%**

Lifetime Risk:
This woman's Risk (to age 85): **18.0%**
Average woman (to age 85): **10.6%**

This woman's estimated risk for developing breast cancer over the next 10 years is 3.3% compared to a risk of 1.9% for a woman of the same age from the general population. The lifetime risk for developing breast cancer (to age 85) is 18.0% compared to a risk of 10.6% for a woman of the same age from the general population. This calculation also means that this woman's chance of remaining breast-cancer free over the next 10 years is 96.7%.

Case

A) Screening breast program with mammograms every 2 years
B) Screening breast program with mammograms yearly
C) Discuss yearly mammograms - Screening breast program with mammograms every 2 years, plus ordering a mammogram in between
D) Yearly mammograms plus yearly ultrasound
E) Do nothing

Precision Screening

Risk Factors in Asymptomatic Patients

Risk Factor	Estimated Maximum Relative Risk
BRCA1 or BRCA2	15x*
Personal history of breast cancer	7x to 10x*
Prior breast biopsy showing certain non-cancerous pathologies	
•Ductal Intra-epithelial Neoplasia (DIN 1b)	5x*
•Lobular Intra-epithelial Neoplasia (LIN)	4x to 10x*
First-degree relative (mother, sister) diagnosed with breast cancer by age 50	2x*
Obesity	1.3x*
Alcohol Use	1.6x*
BI-RADS C (heterogeneously dense)	2.92x†
BI-RADS D (extremely dense)	4.64x†

** Compared to women without this specific risk factor*
† compared to fatty breast density

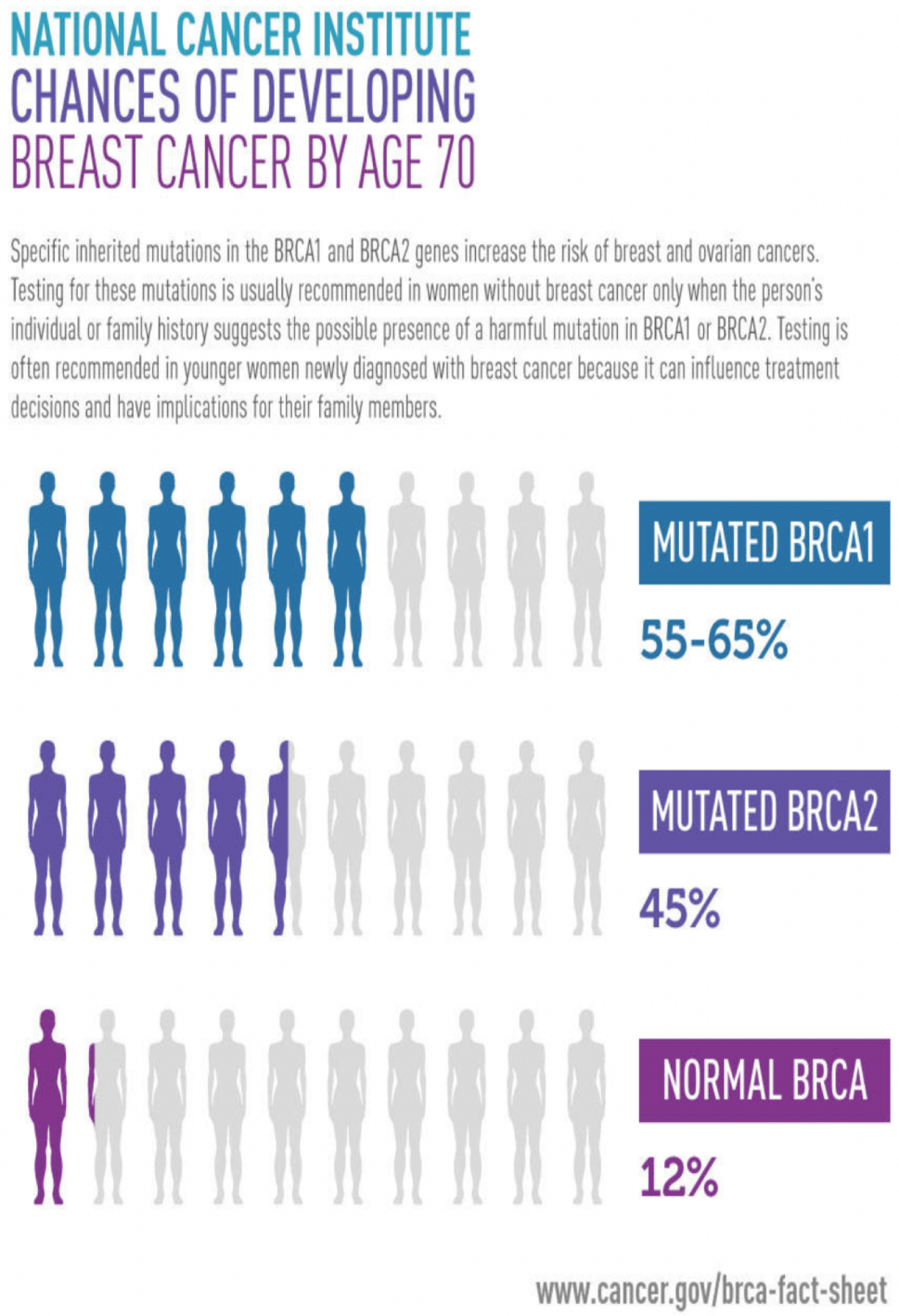
Precision Screening

- Incorporating risk factors in guiding screening recommendations
  - Risk calculators
  - Risk factors:
    - Genetic risk
    - Ethnicity
    - Lifestyle
    - lack of exercise
    - excessive alcohol consumption
    - smoking
    - Obesity
    - Breastfeeding
    - Mammographic density

Genetic risk

- BRCA 1 and 2 genes are involved in repairing DNA
- Inherited mutation are present in 2-3% of breast cancers
- 0.25% of the population would have a mutation

- For women with a strong family history or family member with a BRCA mutation – Genetic counseling and testing is available
- Private testing is also available



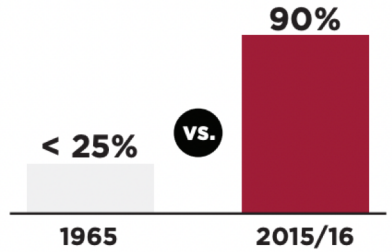
Breastfeeding

- Every 12months of breastfeeding there is a RR reduction for breast cancer of ~4%
- Mechanism – not fully known, however glycoproteins stanniocalcin (STC1) and STC2 are increased during lactation and turn off two well knows oncogenes (PAPP-A and IGFBP5)
- Breastfeeding rates and durations could potential be increased by scaling up already well established programs for lactation support, perceived culture, parental leave, etc.

reference

BREASTFEEDING IN CANADA

Breastfeeding initiation rates in Canada have INCREASED



The most common reasons mothers give for stopping breastfeeding before 6 months are:

- not enough milk
- difficulty with breastfeeding technique

57%

In 2011/12, **OVER HALF** of women who breastfed continued some breastfeeding **beyond 6 months**.

Close to **25%** of women **STOP** breastfeeding before their infant is **one month old**.

Breastfeeding rates also vary across the country along a general west-to-east gradient.

In 2011/12, breastfeeding initiation ranged from **96%** in **British Columbia and Yukon** to **57%** in **Newfoundland and Labrador**.

BABY-FRIENDLY FACILITIES

21 hospitals, 8 birthing centres and **117 community centres** are designated as **BABY-FRIENDLY** facilities in Canada.

Globally only **10% of infants** are born in a hospital designated **BABY-FRIENDLY**.

A hospital providing maternity services or a community health facility is designated as **BABY-FRIENDLY** if it meets the criteria for achieving the **Ten Steps AND adheres to the International Code of Marketing of Breast-milk Substitutes**.

Childbearing (women are having fewer children and later on in life)

- Childbearing prior to 35 provides long term protection against breast cancer
- After 35 the risk of breast cancer is higher than for nulliparous women
- The parity association is for ER-positive breast cancer
- The protection is not immediate, first there is an increased risk (intra and post partum)
- Mechanism – not fully understood (theories include reduced mammary stem cells, changes in the immune microenvironment)

Schedin, P. Pregnancy-associated breast cancer and metastasis. *Nat. Rev. Cancer* **6**, 281–291 (2006).

Obesity and physical activity

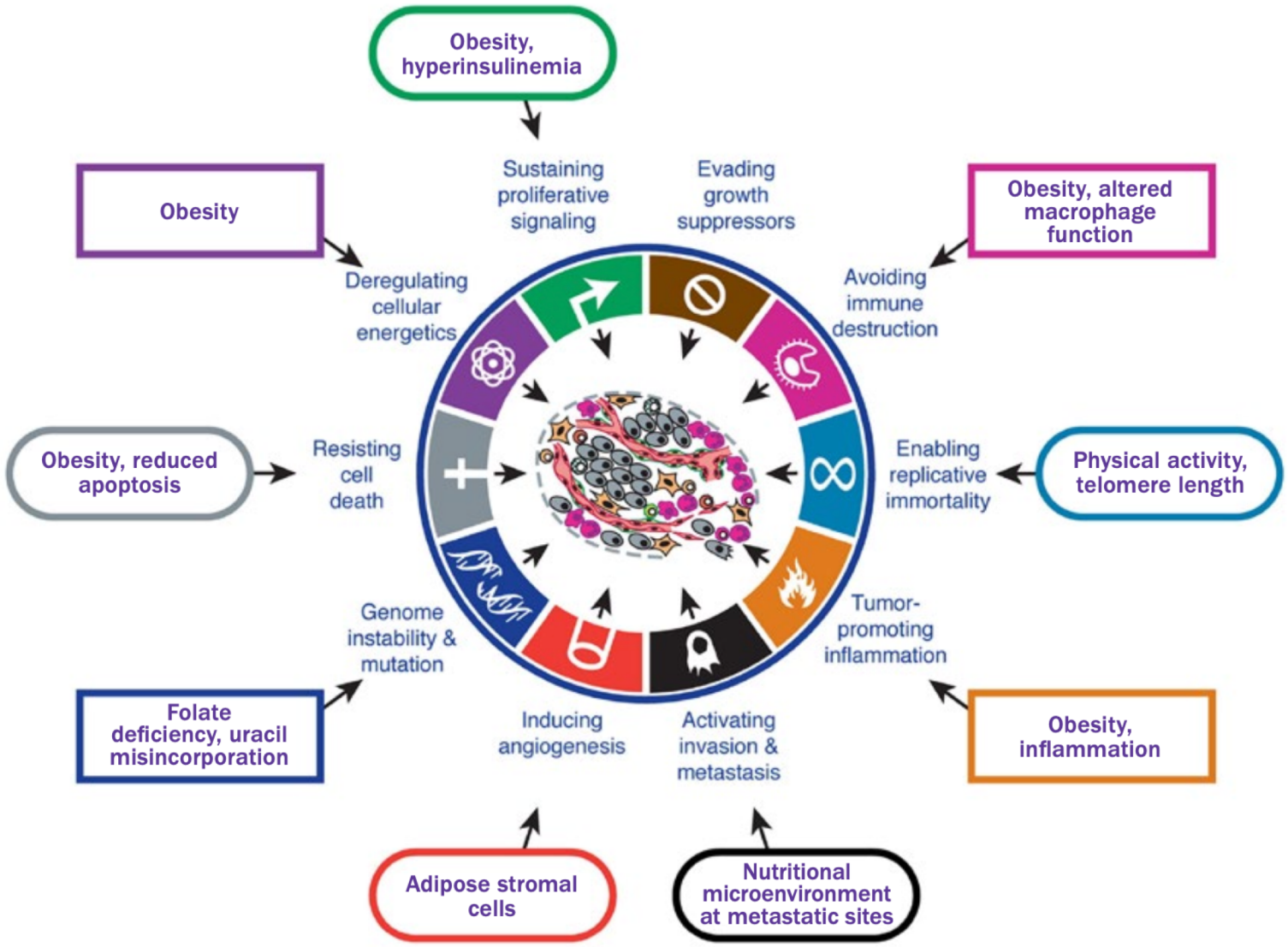
- High BMI in the postmenopausal years is associated with increased breast cancer risk (RR 1.3)
  - Increased estrogens produced by adipose tissue
- Physical activity independent of BMI is associated with a moderate reduction in the risk of developing breast cancer (20% reduction)
- Physical activity improves insulin resistance, reduces fasting insulin

World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Breast Cancer* https://www.wcrf.org/sites/default/files/ Summary-of-Third-Expert-Report-2018.pdf (2018).

Lifestyle

- Limited use of interventional trial data on lifestyle changes
- Observational data is messy! → shouldn't be a reason to not look at it altogether
- Women's Health Initiative – 5% relative risk reduction from dietary modification of reduced fat intake and increased consumption of fruits, vegetables and grains. (HR 0.95 @ 20 year follow-up)

Figure 5: Nutrition, physical activity and the hallmarks of cancer



Adapted from: Cell 144, Hanahan D and Weinberg RA, Hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Breast Cancer* https://www.wcrf.org/sites/default/files/ Summary-of-Third-Expert-Report-2018.pdf (2018).

Alcohol

- Class I carcinogen (International Agency for Research on Cancer)
- Safest level of intake = NONE
- Mechanisms
  - Ethanol stimulates proliferation and activity of the ligand-activated ER pathway → increases estrogen levels
  - Ethanol in blood can also be converted to acetaldehyde (by ADH) → acetaldehyde causes DNA damage
  - Suppresses immune function

Britt, K.L., Cuzick, J. & Phillips, KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer* **20,** 417–436 (2020). https://doi.org/10.1038/s41568-020-0266-x

Hormone Replacement Therapy

- Research shows that taking hormone replacement therapy (HRT) for a long time increases the risk of breast cancer. This is especially true for HRT that uses estrogen plus progestin (called combined HRT).
- Researchers looked at the data from numerous studies. Their analysis showed that current or recent users of combined HRT for 5 years or longer have a higher risk for breast cancer.
- The Women's Health Initiative (WHI) study showed the risk for breast cancer went up by about 1% for every year that women took estrogen alone and about 8% for every year that they took combined HRT. The study also found that the risk was increased even with comparatively short-term use of combined HRT compared to a placebo. The higher risk appears to disappear a few years after stopping HRT.
- The WHI study also showed that there was a significant drop in the rate of new cases of breast cancer from 2002 to 2004 among Canadian women aged 50–69 years.
- Every HRT type, **except vaginal estrogens**, increased the breast cancer risk (compared with non-users), which steadily rose with duration of use and was greater for estrogen and progestogen preparations (combined mHt) than oestrogen-only ones.

https://cancer.ca/en/cancer-information/cancer-types/breast/risks

Risk Calculators

- Many are available.
- Attempt to quantify the combined effect of many of the breast cancer risk factors we have discussed
- Important that they are independently validated

- My preferred one is the IBIS model, it is the most encompassing

https://ibis.ikonopedia.com/

Model input	Risk estimation model				
	BCRAT[160,162]	IBIS[163,165]	BRCAPRO[a159,161,259]	BCSC[164]	BOADICEA[157,158]
Individual factors					
Age	≥35	+	+	+	+
Race or ethnicity	+	+	+	+	+
Age at menarche	+	+	NA	NA	NA
Age at menopause	NA	+	NA	NA	NA
Age at first birth	+	+	NA	NA	NA
Parity	NA	+	NA	NA	NA
BMI	NA	+	NA	NA	NA
Hormonal contraception use	NA	NA	NA	NA	NA
MHT use	NA	+	NA	NA	NA
Alcohol use	NA	NA	NA	NA	NA
Breast-related factors					
Number of prior breast biopsies	+	+	NA	+	NA
Atypical hyperplasia	+	+	NA	NA	NA
LCIS	NA	+	NA	NA	NA
Other benign pathology	NA	+	NA	NA	NA
Mammographic density	NA	+	NA	+	NA
Therapeutic irradiation[b]	NA	NA	NA	NA	NA
Genetic testing					
BRCA1 or *BRCA2*	NA	+	+	NA	+
Other high-risk genes	NA	NA	NA	NA	+
SNPs or polygenic risk score	NA	+	NA	NA	–[c]
FHx factors[d]					
Cancer status of first-degree relatives	+	+	+	+	+
Cancer status of second-degree relatives	NA	+	+	NA	+[d]
Age at breast cancer diagnosis	NA	+	+	NA	+
Pathology of breast cancer	NA	NA	+	NA	+
Bilateral breast cancer	NA	+	+	NA	+
Male breast cancer	NA	+	+	NA	+
Ovarian cancer	NA	+	+	NA	+
Pancreatic and prostate cancer	NA	NA	NA	NA	+
Genetic testing	NA	+	+	NA	+
Mastectomy status	NA	NA	+	NA	NA
Oophorectomy status	NA	NA	+	NA	NA

Britt, K.L., Cuzick, J. & Phillips, KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer* **20,** 417–436 (2020). https://doi.org/10.1038/s41568-020-0266-x

Prevention

- Most of the world and Canada has focused on prevention strategies on untargeted, population-based educational interventions
  - Increasing physical activity
  - Reducing BMI
  - Alcohol intake
- In the primary care setting these interventions also reduce the risk of other important causes of mortality
- Augmenting this is the next step

Precision breast cancer prevention

- GOAL – intervene with the right tool, at the right time, to the right population
- FIRST STEP – knowing your risk
  - Using risk calculators like IBIS. These will improve with time.
- SECOND STEP – advocacy
  - Screening mammograms (finding the right frequency and when to start)
  - Considering additional screening for higher risk populations
  - Guidelines for high risk women
  - Awareness that the landscape is changing

Hig)

Professional body	Intervention			
	RRBM	RRSO	Medication[a]	Lifestyle factors
NCCN[188]	Consider for: high-risk breast cancer gene mutation; compelling FHx; prior thoracic RT below the age of 30 years	Controversy over whether RRSO reduces breast cancer risk for BRCA mutation carriers but, based on the OC risk, recommend for: *BRCA1* between age 35 and 40 years; *BRCA2* between age 40 and 45 years. Exercise caution in prescribing HRT post RRSO	Offer if: ≥35 years old with 5-year breast cancer risk ≥1.7%; have LCIS. Premenopausal: tamoxifen; postmenopausal: tamoxifen, raloxifene, exemestane or anastrozole	MHT (consider associated breast cancer risk); alcohol (limit consumption); exercise (premenopausal: vigorous; postmenopausal: moderate to vigorous); healthy weight; breastfeeding
NICE[189]	Consider for: lifetime risk ≥30%	Consider for: lifetime risk ≥30%; offer MHT up until age of natural menopause — oestrogen alone if prior hysterectomy, combined MHT otherwise	Consider if: lifetime risk ≥17%. Premenopausal: tamoxifen; postmenopausal: anastrozole (unless severe osteoporosis), tamoxifen (if severe osteoporosis or if the individual does not want to take anastrozole) or raloxifene (if the individual does not want to take tamoxifen)	OCP (if >35 years old inform of increased risk of breast cancer; for *BRCA1* mutation carriers, discuss potential increased risk of breast cancer before age 40 years); breastfeeding; MHT (advise of increased breast cancer risk; tailor use to individual circumstances; use lowest dose for shortest time possible (generally not after age 50 years); prescribe oestrogen without progesterone if hysterectomy); alcohol (advise of increased breast cancer risk); smoking (advise cessation); healthy weight; exercise
ASCO[190]	NA	NA	Consider if: ≥35 years old with 5-year risk ≥1.66 or have LCIS. Premenopausal: tamoxifen; postmenopausal: raloxifene, exemestane or anastrozole	NA

ACSO, American Society of Clinical Oncology; FHx, family history; HRT, hormone replacement therapy; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy; NA, not applicable; NCCN, (US) National Comprehensive Cancer Network; NICE, (UK) National Institute for Health and Care Excellence; OC, ovarian cancer; OCP, oral contraceptive pill; RRBM, risk-reducing bilateral mastectomy; RRSO, risk-reducing bilateral salpingo-oophorectomy; RT, radiotherapy. [a]A 5-year course; no guideline currently recommends a 3-year lower-dose course as tested by DeCensi et al.[224], although ASCO guidelines suggest that women who stop tamoxifen after 3 years will likely still derive benefit and that for women with intraepithelial neoplasia the low dose of tamoxifen (5 mg per day) may be an alternative if there are concerns over adverse events with the higher dose.

Britt, K.L., Cuzick, J. & Phillips, KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer* **20,** 417–436 (2020). https://doi.org/10.1038/s41568-020-0266-x

Risk reducing medication

- Options for patients not wanting to underego mastectomy
- Those whose risk is increased but not elevated enough for surgery to be appropriate
- None have been shown to decrease breast cancer mortality
- Reduce the risk of ER- positive breast cancer
- Given to avoid breast cancer diagnosis and subsequent treatment even though the subsequent treatment not resulting premature mortality

Tamoxifen, Raloxifene, Exemestane

- Tamoxifen - reduces the risk of developing primary breast cancer by 50%. In the largest study, among 13,388 women randomized to tamoxifen or placebo, DCIS and invasive breast cancer occurred in the 244 placebo group and 124 in the tamoxifen group over a 5.5 year period.
- Side effects = endometrial cancer from 0.09% increased to 0.23%, a small increase in the incidence of stroke, from 0.36% to 0.58%, and of deep venous thrombosis (0.08 vs 0.13% per year). Other primary prevention studies have shown similar effects.
- Raloxifene similar data (less vaginal bleeding, endometrial cancer)
- Exemestane – 65% reduced risk or ER+ breast cancer (in postmenopausal women) (0.55% annual incidence rate of breast cancer compared with 0.19%) Side effects- Joint pain.

Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Fisher B, Costantino JP, Wickerham DL, et al. Journal of the National Cancer Institute, 90 (18), 1998

Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial:Preventing Breast Cancer. Vogel VG, Costantino JP, Wickerham DL, et al. Cancer Prev Res; 3(6); 696–706, 2010.

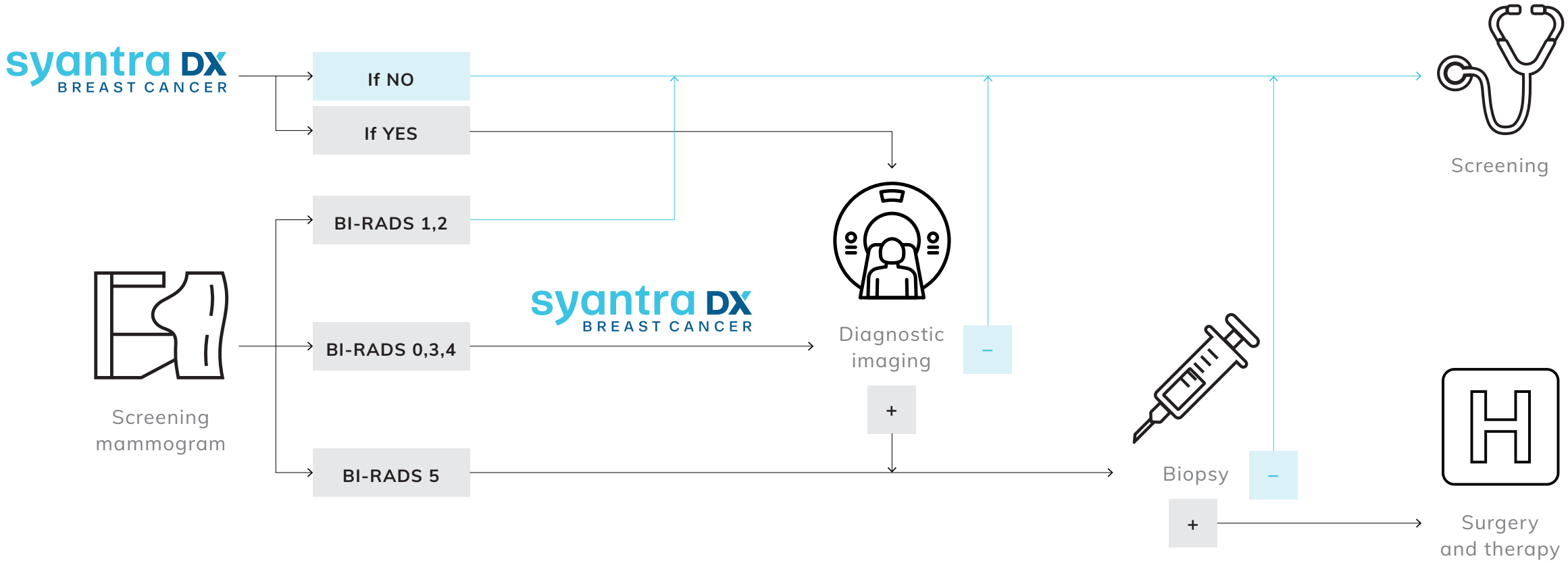
Exemestane for Breast-Cancer Prevention in Postmenopausal Women Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E Alés-Martínez, This article (10.1056/NEJMoa1103507) was published on June 4, 2011, at NEJM.org. N Engl J Med 2011.

Uptake is low…

- Physician related
  - Who should be doing the prescribing – no clarity? Initiating and discussing
  - Clinicians have difficulty assessing breast cancer risk
  - Lack of commercial interest in prevention
- Patient related
  - Fear of side effects
  - “cancer drug” stigma

Potential breast cancer detection journey with Syantra DX

Supplements mammography, potentially more people getting screened



*Definitive breast cancer diagnosis must be provided by pathology analysis of biopsy specimen

Syantra DX validation

Test may perform well for detecting the absence or presence of breast cancer[1]

Women aged 25-80 (whole cohort)

92.2%
Accuracy

94.3%
Specificity
Ability to detect “no cancer”

79.2%
Sensitivity
Ability to detect “cancer”

Women under 50 years old

98.5%
Accuracy

99.0%
Specificity
Ability to detect “no cancer”

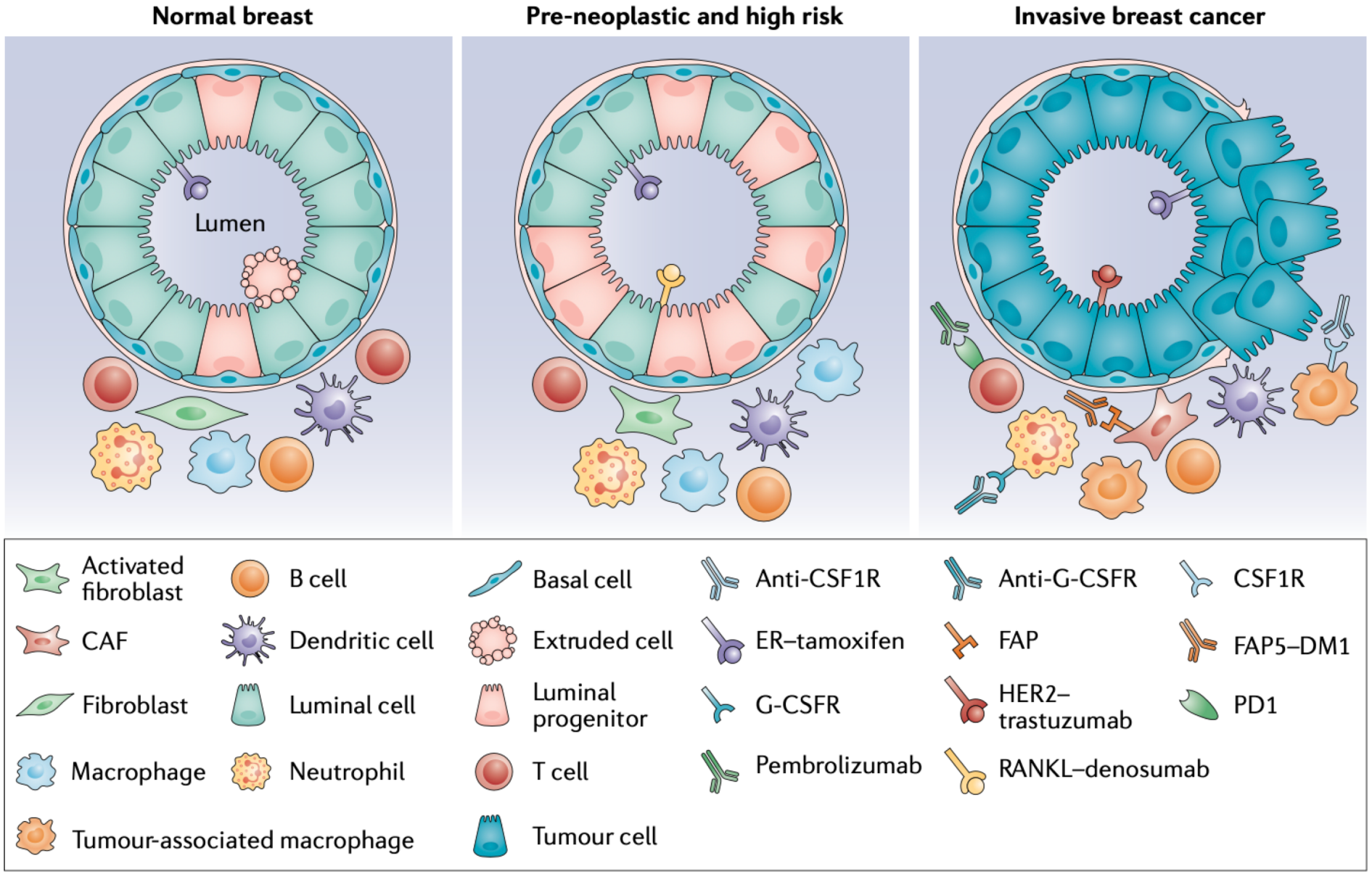
91.7%
Sensitivity
Ability to detect “cancer”

Not tested in women with breast surgery in past year or with previous cancer diagnosis

[1]Inferred results from ongoing clinical study presented at SABCS 2021; NCT04495244; clinicaltrials.gov; 1,107 participants; 99.5% confidence intervals

Investigational

- Metformin
- RANKL inhibitors
- Bisphosphonates



Britt, K.L., Cuzick, J. & Phillips, KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer* **20,** 417–436 (2020). https://doi.org/10.1038/s41568-020-0266-x

Thank you