Breast Cancer in 2023

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Disclosures

- No financial disclosures

- But…I am a surgical oncologist

Outline

- Screening
- Risk Assessment
- Evaluation
- Treatment
  - Surgical therapy
  - Systemic therapy
  - Radiation therapy
- Survivorship

Breast Cancer Screening

- American Cancer Society
  - Women ages 40-44: Option for annual mammogram
  - Women ages 45-55: Annual mammogram
  - Women ages 55+: Option to switch to every 2 years or continue annual
  - Screening mammograms should stop when life expectancy < 10 years
- American Society of Breast Surgeons
  - Women ages 40+: Annual mammogram
  - Screening mammograms should stop when life expectancy < 10 years
  - Women ages 25+: Should undergo formal risk assessment and update at regular intervals
  - Supplemental screening for women at higher-than-average risk
- US Preventative Services Task Force
  - Women ages 40-49: Based on individual decision
  - Women ages 50-74: Every 2 years
  - Women ages 75+: Unable to weight benefits vs harms

Note – USPSTF issued draft recommendation statement that all women should get screened for breast cancer every other year, starting at age 40.

Current Oncology

MDPI

Article

The Impact of Organised Screening Programs on Breast Cancer Stage at Diagnosis for Canadian Women Aged 40–49 and 50–59

- Breast cancer incidence and stage at presentation was compared between Canadian provinces with screening of women < 50 to those that did not screen.
- Women 40-49 in provinces without screening were more likely to be dx with stage II, III, and IV breast cancer
  - Stage II BC: 43.7% vs 40.7%, p<0.001
  - Stage III BC: 18.3% vs 15.6%, p<0.001
  - Stage IV BC: 4.6% vs 3.9%, p=0.001
- Women 40-49 undergoing screening had more Stage I breast cancer
  - Stage I BC: 39/9% vs 33.3%, p<0.001

Curr Oncol. 2022 29(8):5627-5643.

Current Oncology

MDPI

Article

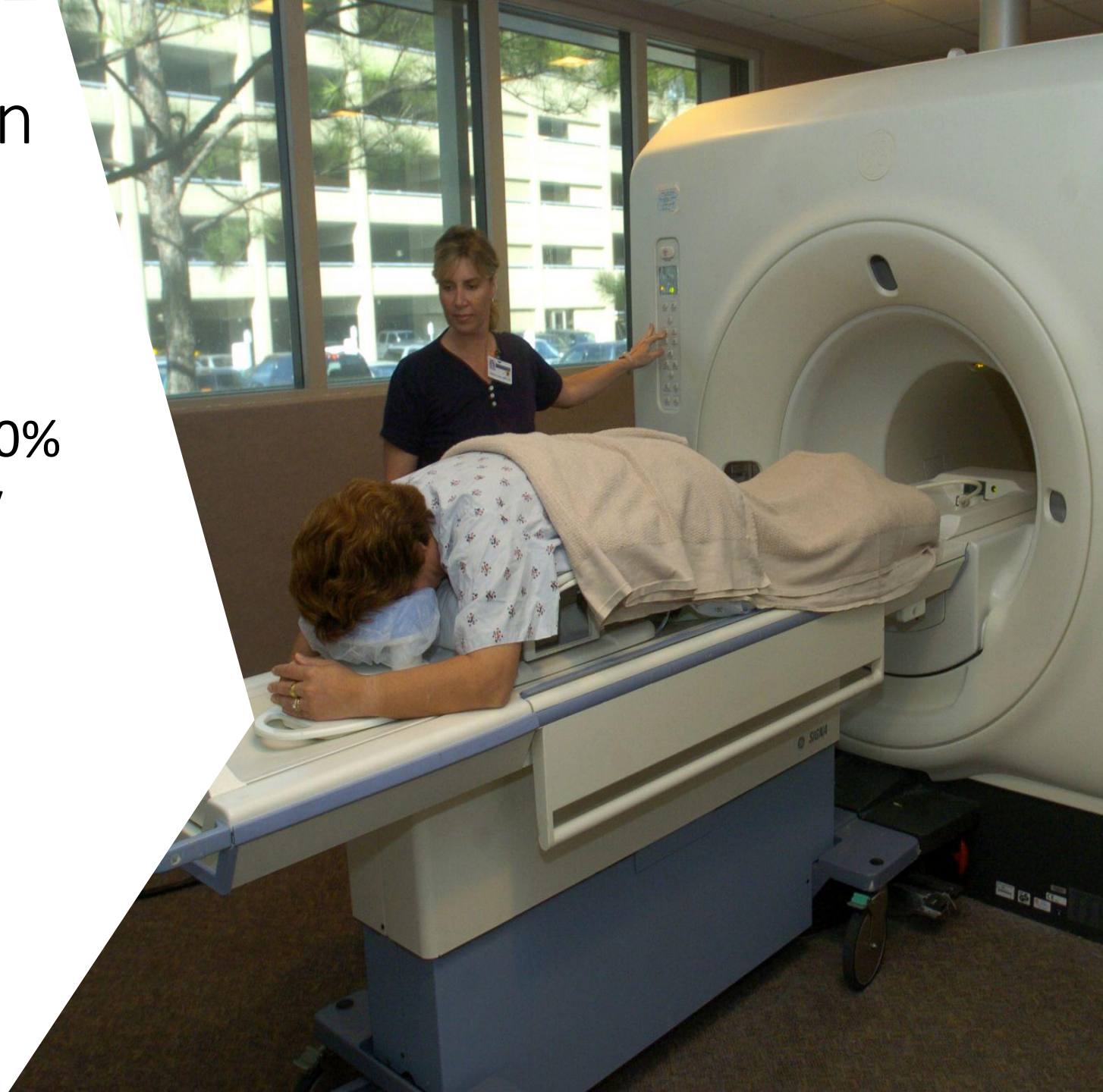
The Impact of Organised Screening Programs on Breast Cancer Stage at Diagnosis for Canadian Women Aged 40–49 and 50–59

- Provinces without screening at 40-49 had stage migration in women 50-59.
  - Higher rates of Stage II, III, IV
    - Stage II BC: 37.2% vs 36.0%, p=0.003
    - Stage III BC: 13.6% vs 12.3%, p<0.001
    - Stage IV BC: 4.6% vs 3.9%, p=0.001
  - Lower rate of Stage I
    - Stage I BC: 44.5% vs 46.8%, p<0.001
- Although the incidence of BC is low in women 40-49, excluding those women from screening negatively impacts women 40-49 and 50-59.
- Focus not on harms of screening but on harms of not screening women 40-49

Curr Oncol. 2022 29(8):5627-5643.

Who needs more than a mammogram?

- Elevated risk of breast cancer (Defined as a lifetime risk ≥ 20% using models based on family history)
- Thoracic radiation therapy between ages 10-30



Risk Assessment

Model	Family history	Personal history	Other risk factors	Genetics	Purpose	Not applicable for	Calculated risk
Gail or BCRAT	1st degree female relatives	Breast biopsies including ADH/ALH	Age at menarche, 1st live birth, menopause	None	Chemoprevention if 5-yr risk > 1.67%	Personal history of BC, DCIS, LCIS; 2nd/3rd degree or male relatives, < age 35, prior chest radiation, known genetic mutations	Lifetime risk to 90 y/o; 5-yr risk for invasive cancer
Claus	1st/2nd degree female relatives including age of onset. Includes 2 affected relatives only	None	None	1 autosomal dominant gene for age-dependent penetrance	Breast MRI screening	Personal history of BC, DCIS, LCIS; > 2 affected relatives, affected male relatives, prior chest radiation, known genetic mutation	Lifetime risk to 79 y/o for DCIS and invasive cancer
Tyrer-Cuzick Model	1st/2nd/3rd degree relatives with age of onset and bilateral BC, includes family size and unaffected; also includes history of ovarian cancer	Breast biopsies including ALH, ADH, LCIS	Age of menarche, 1st live birth, menopause, HRT use, breast density, BMI	BRCA and multiple genes of varying penetrance	Breast MRI screening	Very strong family history or early-onset BC in multiple relatives, chest radiation, non-white race	Lifetime risk to 85 y/o and 10 yr risk for DCIS and invasive BC; risk of BRCA1/2 gene mutation

American Journal of Roentgenology. 2019;212: 250-258. 10.2214/AJR.18.20345

Breast Cancer Screening for Women at Higher-Than-Average Risk: Updated Recommendations From the ACR

Population at Risk	Prior Recommendation (2018) (Starting Age)	Current Recommendation (2023) (Starting Age)
Genetic mutation carriers/untested first-degree relatives	▪ Annual DM ± DBT (age 30) ▪ BRCA1 only DM ± DBT exception ▪ Annual MRI (age 25-30)	▪ Annual DM ± DBT (**age 40 if annual MRI**; age 30 if not) ▪ Annual MRI (25-30 y)
Calculated lifetime risk of ≥20%	▪ Annual DM ± DBT ▪ Annual MRI (Age 30)	▪ Annual DM ± DBT ▪ Annual MRI (Age 30)
History of chest/abdominal radiation treatment at a young age	▪ Annual DM ± DBT ▪ Annual MRI (Age 25 or 8 y after treatment, whichever is later)	▪ Annual DM ± DBT ▪ Annual MRI ▪ **Consider abdominal RT that overlaps breast in risk** (Age 25 or 8 y after treatment, whichever is later)
PH of breast cancer before age 40	▪ Annual DM ± DBT ▪ Annual MRI if dense breasts or if diagnosed before age 50; others with PH consider MRI (From age at diagnosis)	▪ Annual DM ± DBT ▪ Annual MRI if dense breasts or if diagnosed before age 50; others with PH consider MRI (From age at diagnosis)
History of atypia/LCIS diagnosed before age 40	▪ Annual DM ± DBT ▪ Consider annual MRI if other risk factors (From age at diagnosis)	▪ Annual DM ± DBT ▪ Consider annual MRI if other risk factors (From age at diagnosis)
Dense breast tissue	▪ Annual DM ± DBT ▪ Consider annual MRI or ultrasound (Age 40 or earlier if other risk factors)	▪ Annual DM ± DBT ▪ **Annual MRI** ▪ **Consider CEM or ultrasound as alternative to MRI** (Age 40 or earlier if other risk factors)
All women, especially Black, minority, and those of Ashkenazi Jewish descent	Risk assessment by age 30	**Risk assessment by age 25**

J Am Coll Radiol 2023 May 5;S1546-1440(23)00334-4.

What is “right” answer about breast cancer screening?

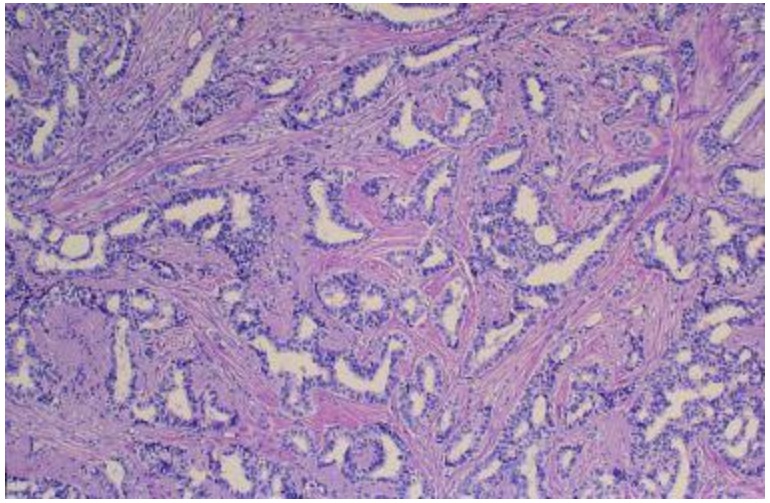
Risk Assessment	All women should understand their risk
Personalized	Breast cancer screening should be based on individual risk and goals
Understand	Understand limitations of breast cancer screening

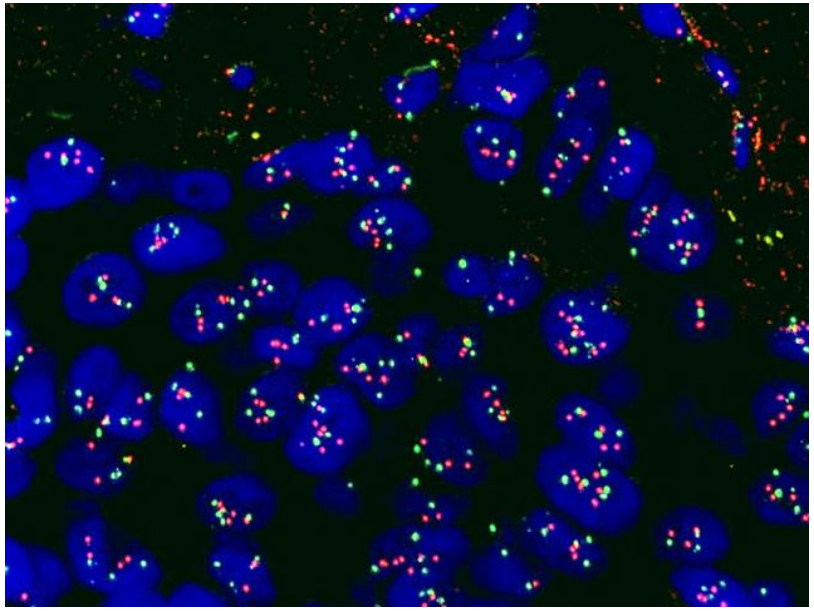
Breast Cancer Diagnosis

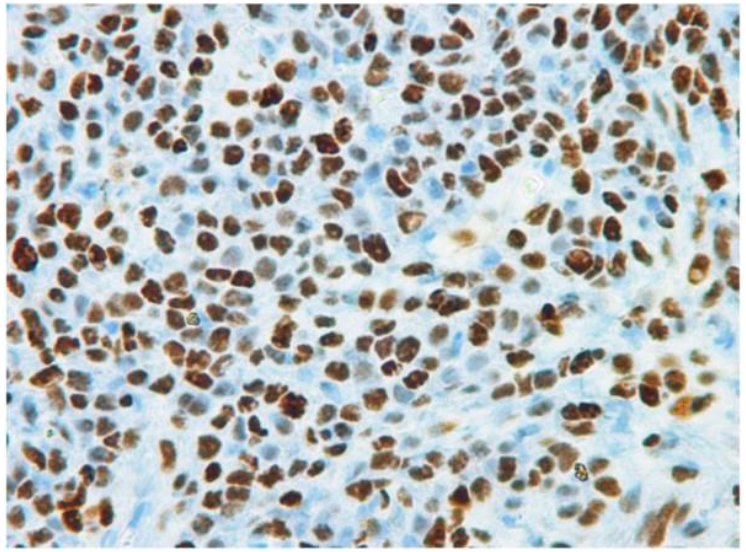
- Pathology Results
- Staging

Biopsy Results

- Tissue histology
- Special stains
  - ER
  - PR
  - HER2
  - Ki 67



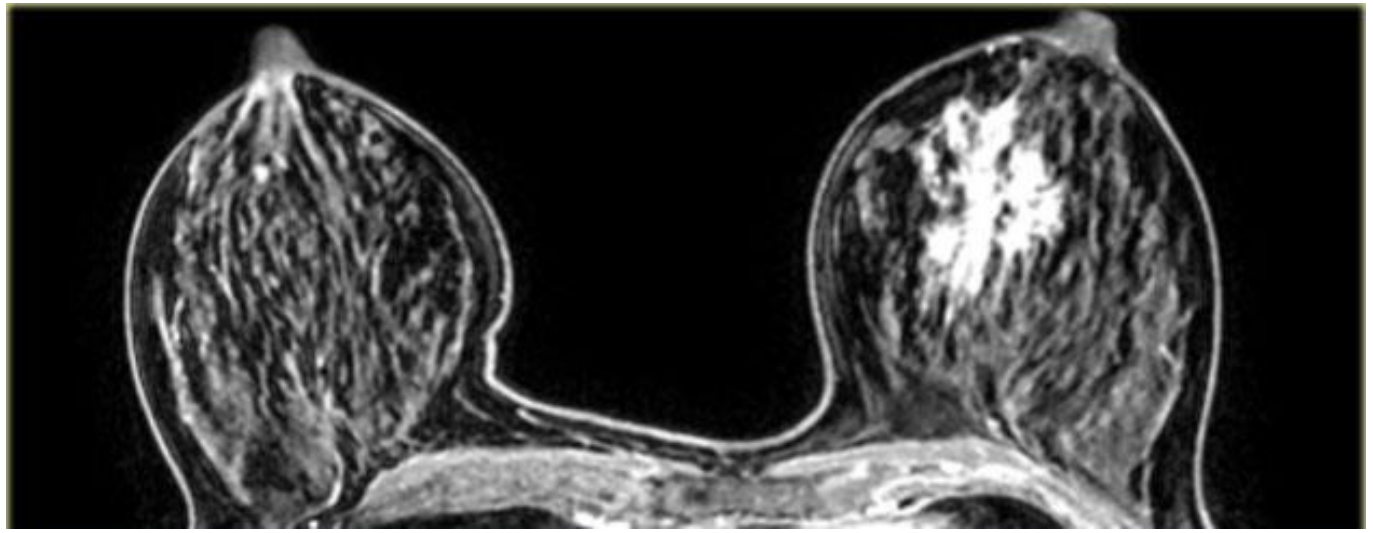




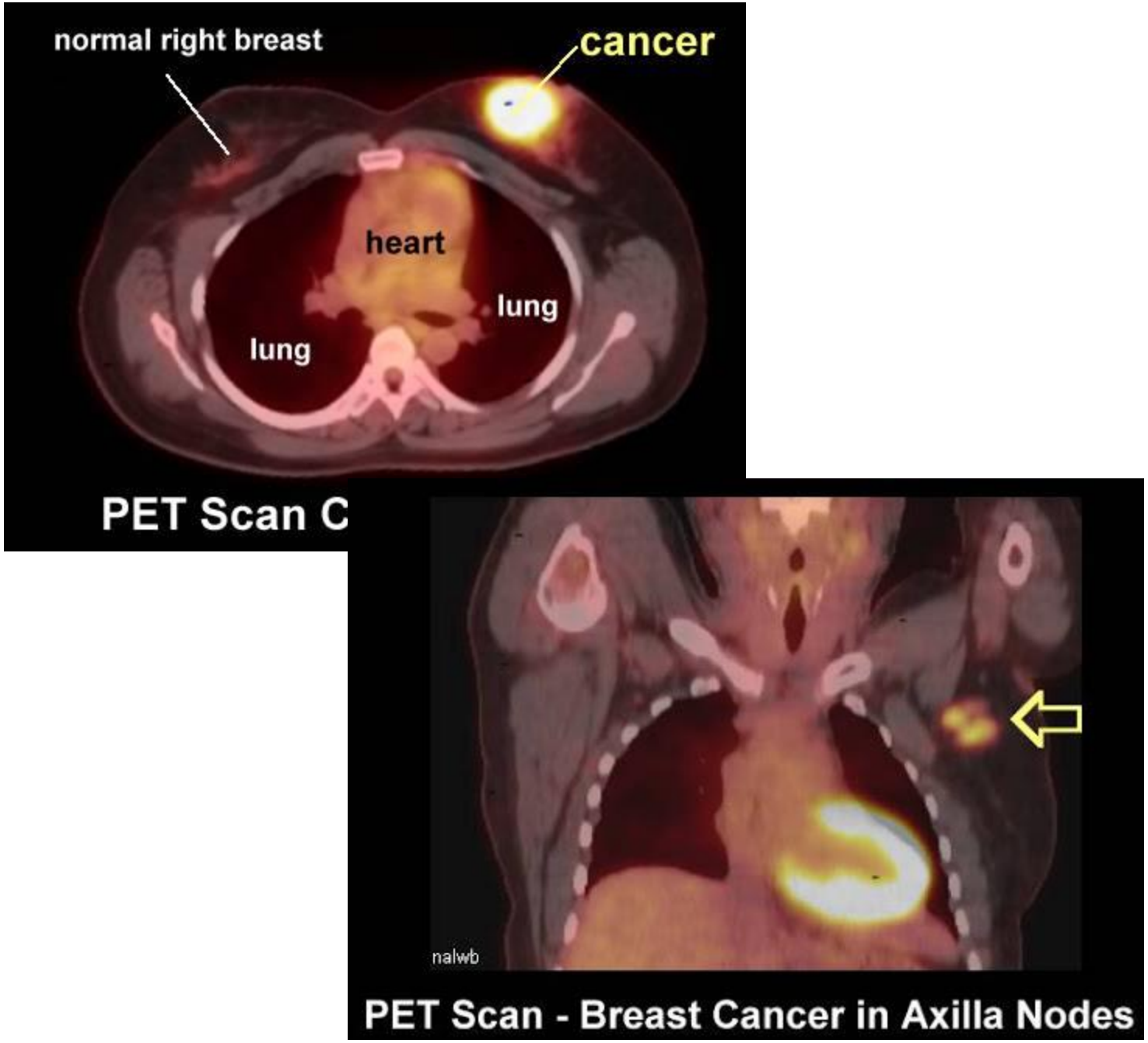
Biologic Subtypes

- 4 main subtypes
  - HR+/HER2-
  - HR+/HER2+
  - HR-/HER2+
  - HR-/HER2- (triple negative)

Breast MRI



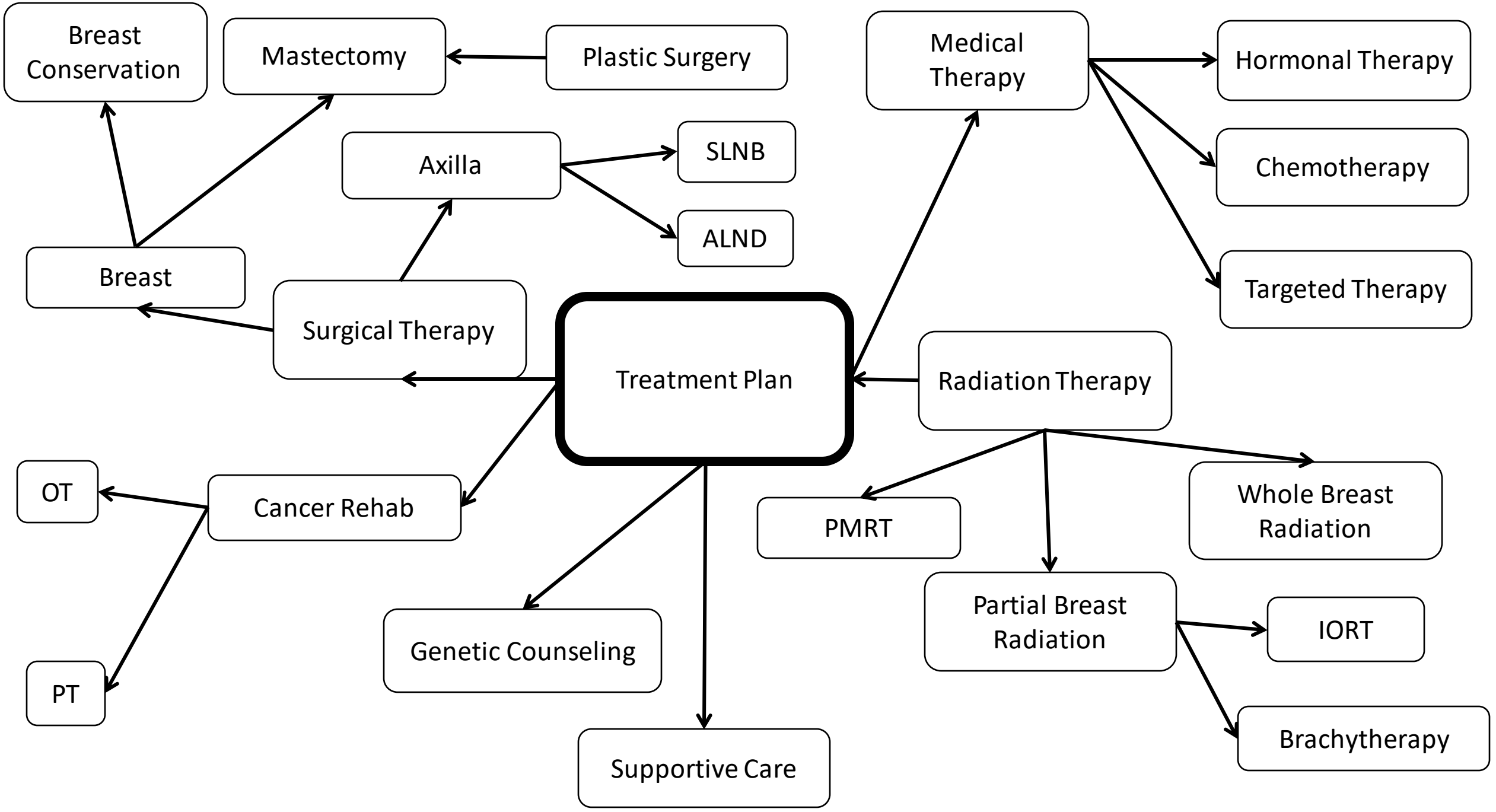
Systemic staging



Staging

- AJCC Staging, updated Jan 2018, Eighth Edition
- 7 Factors
  - T stage – size of tumor
  - N stage – nodal disease
  - M stage – distant sites
  - ER status
  - PR status
  - HER2 status
  - Grade

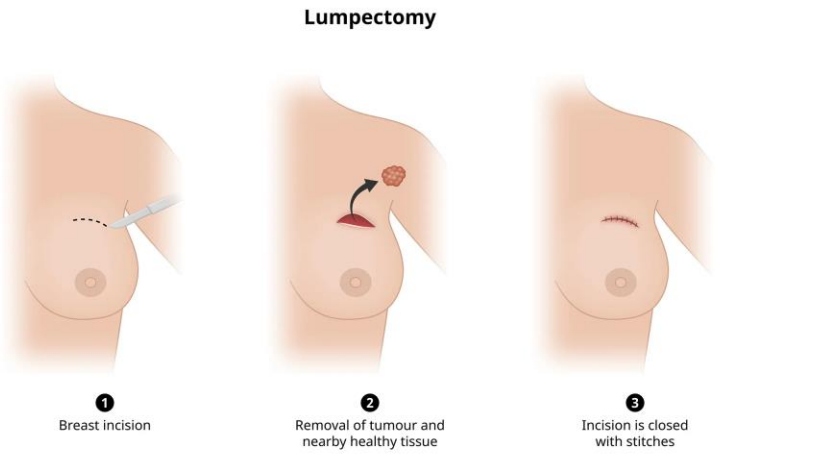
  - The Oncotype Dx Recurrence score can also be considered for pathologic staging


Breast Conservation
Mastectomy
Plastic Surgery
Axilla
SLNB
ALND
Breast
Surgical Therapy
Medical Therapy
Hormonal Therapy
Chemotherapy
Targeted Therapy
Treatment Plan
Radiation Therapy
OT
Cancer Rehab
PT
Genetic Counseling
Supportive Care
PMRT
Whole Breast Radiation
Partial Breast Radiation
IORT
Brachytherapy

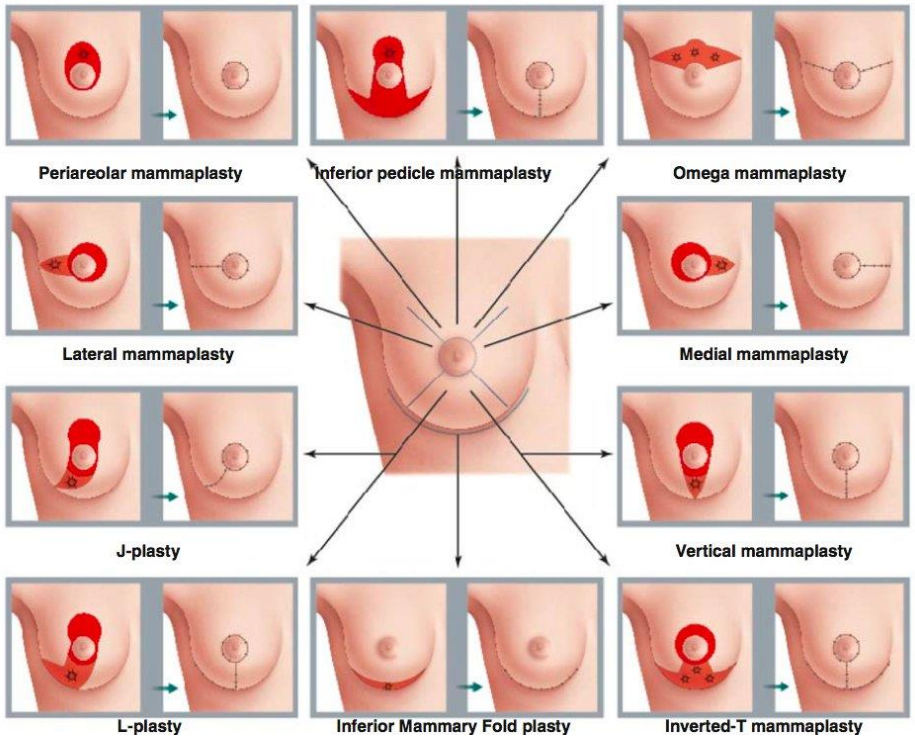
One size doesn't fit all.

Surgical Therapy

Lumpectomy



Oncoplastic Lumpectomy



Mastectomy with reconstruction

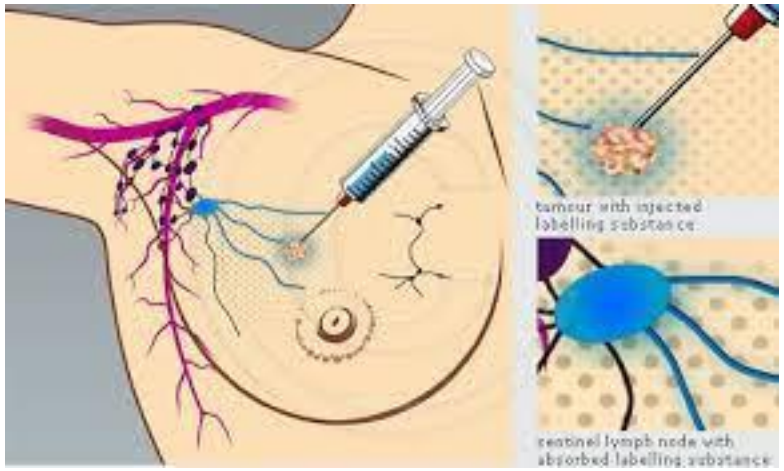
Mastectomy

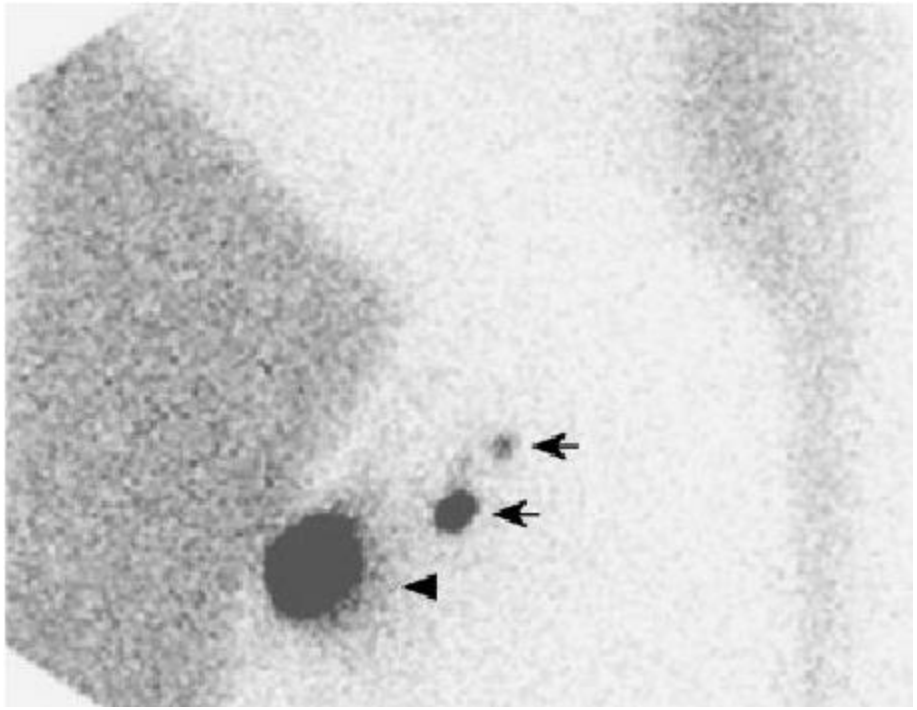
Key Clinical Trials – Breast Management

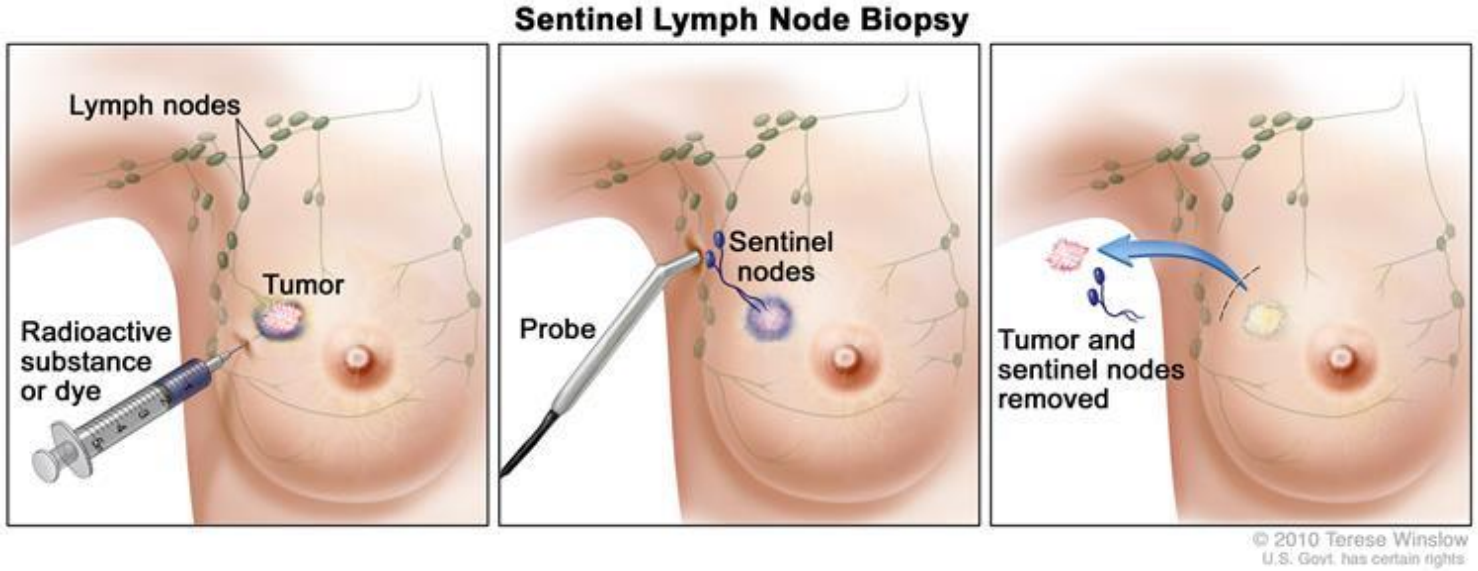
- NSABP B06 (1976-1984) : No difference in DFS or OS at 20 years when comparing mastectomy, lumpectomy, or lumpectomy+RT
  - In breast recurrence 14% in lumpectomy+ RT compared to 39% in lumpectomy
- ACOSOG Z11102 (2012-2016)
  - Single arm trial of BCS+RT in women with 2 or 3 sites of breast cancer in same breast
  - At median f/u 66.4 months – 5 yr LRR 3.1%
  - LRR was increased without pre-op MRI (22.6% vs 1.7%)

Axillary Management

- Move towards removal of less lymph nodes







Key Clinical Trials – Axillary Management

- NSABP B-04 (1971- 1974):
  - Clinically Node Negative: No difference in DFS or OS at 25 yrs of follow-up when comparing radical mastectomy, total mastectomy + RT, and total mastectomy
  - Clinically Node Positive: No difference in DFS or OS comparing radical mastectomy and total mastectomy + RT
  - Estimated that of those who were clinically node negative, approximately 40% of those who had mastectomy alone had positive nodes not removed. However, only 18.6% had an axillary recurrence and no dif in DFS/OR. Thus…evidence that leaving positive nodes did not significantly increase rate of distant recurrence
- NSABP B-32 (1999-2005)
  - No difference in OS, DFS, or regional control in women who underwent a negative SLNB vs ALND
- ACOSOG Z0011 (1999-2004)
  - No difference in OS in women with 1-2 positive SLNs who underwent BCS+RT with or without ALND
- AMAROS (2001-2010)
  - No difference in OS, DFS, and locoregional control at 10-year follow-up comparing axillary RT and ALND in women with 1-3 positive SLNs

Systemic Therapy

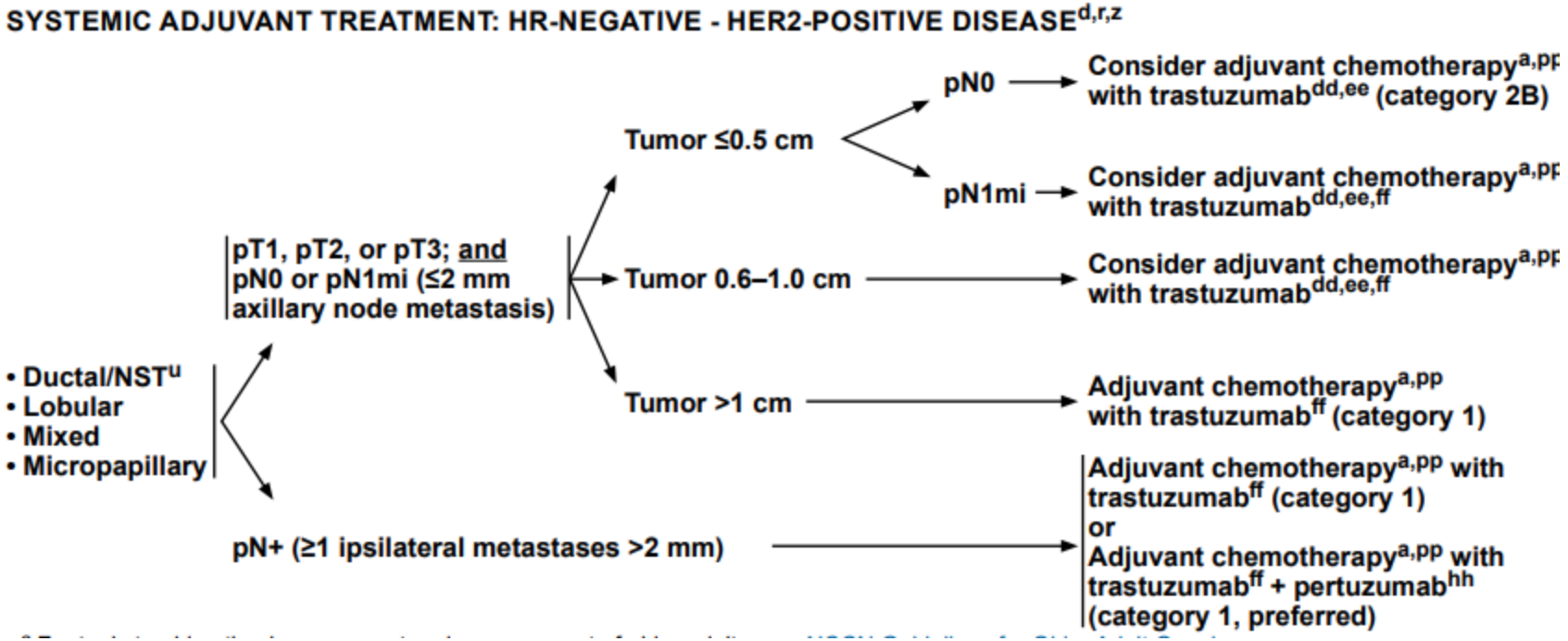
- Endocrine therapy
- Chemotherapy
- Targeted therapy
- Immunotherapy

Endocrine/Hormonal Therapy

- Selective Estrogen Receptor Modulators (SERM)
  - **Tamoxifen**
  - Raloxifene
  - Toremifene
- Aromatase Inhibitors
  - **Letrozole**
  - **Anastrozole**
  - **Exemestane**
- Steroidal Antiestrogens
  - Fulvestrant

Indications for chemotherapy

- Based on risk of recurrence
  - Tumor biology
    - HER2 positive
    - Triple negative
  - Genomics



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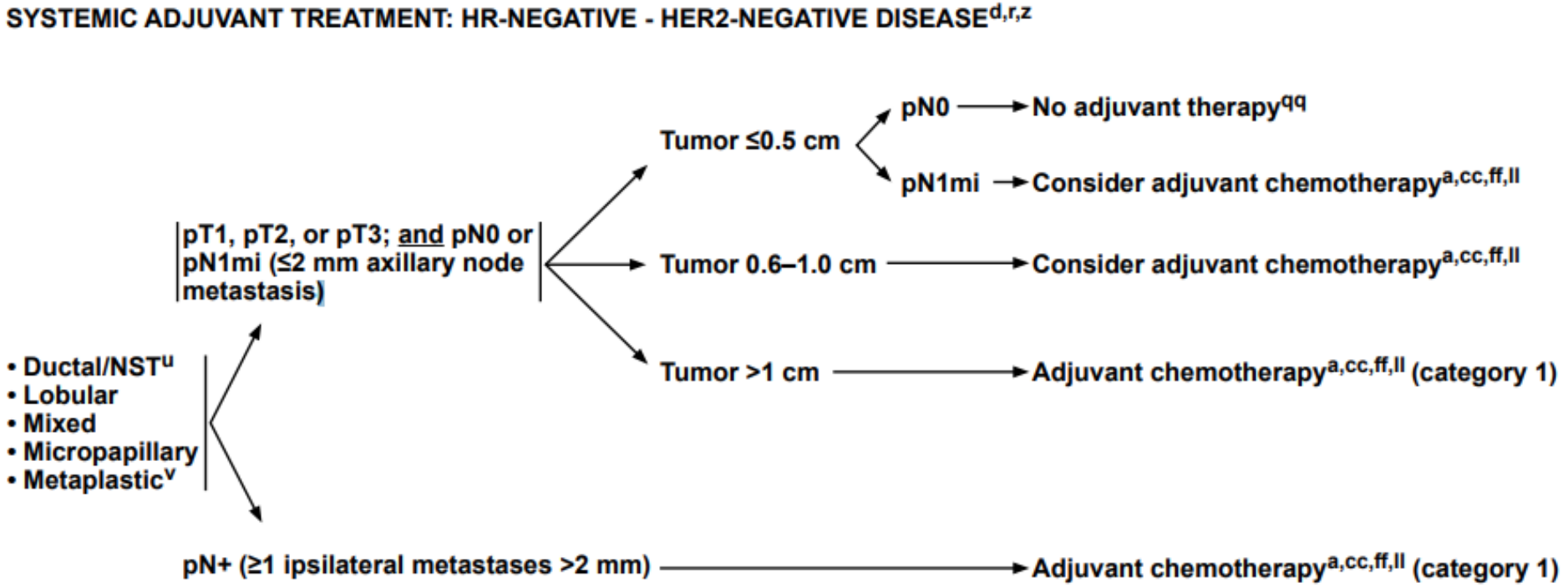
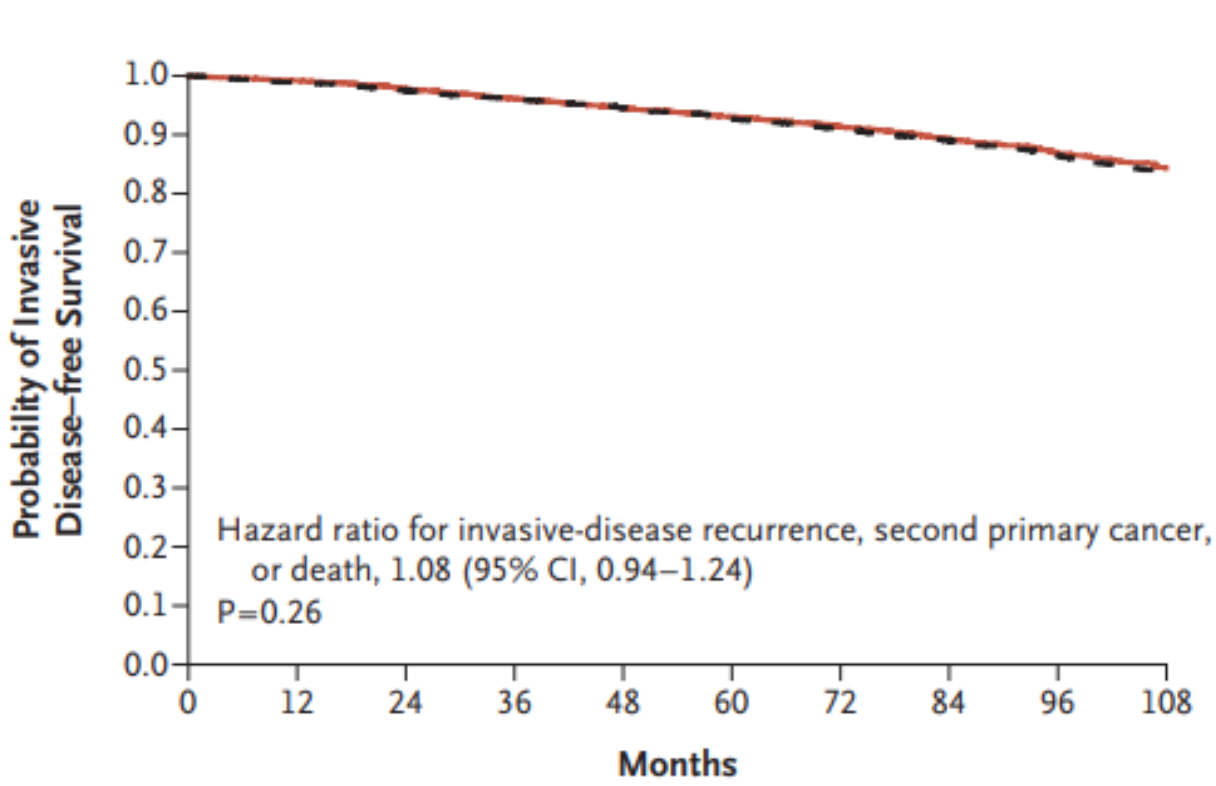


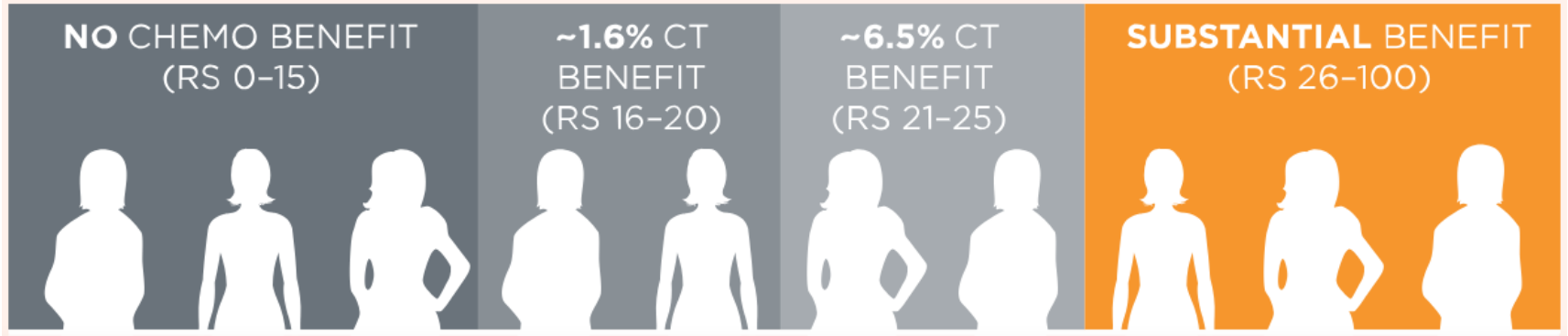
21-Gene Recurrence Score

- Commercially available gene-expression assay
- Provided prognostic information
- Scores range 0-100
- Predictive of chemotherapy benefit (Score ≥ 26) and no benefit in low scores (0-10)

TAILORx

- Designed to address chemotherapy benefit in women HR+/HER2-, node negative breast cancer with intermediate recurrence score (11-25)
- Randomized to either endocrine therapy along or endocrine therapy and chemotherapy
- No benefit to chemotherapy in women with intermediate risk (11-25)
- Subgroup analysis showed some chemotherapy benefit in women aged ≤ 50

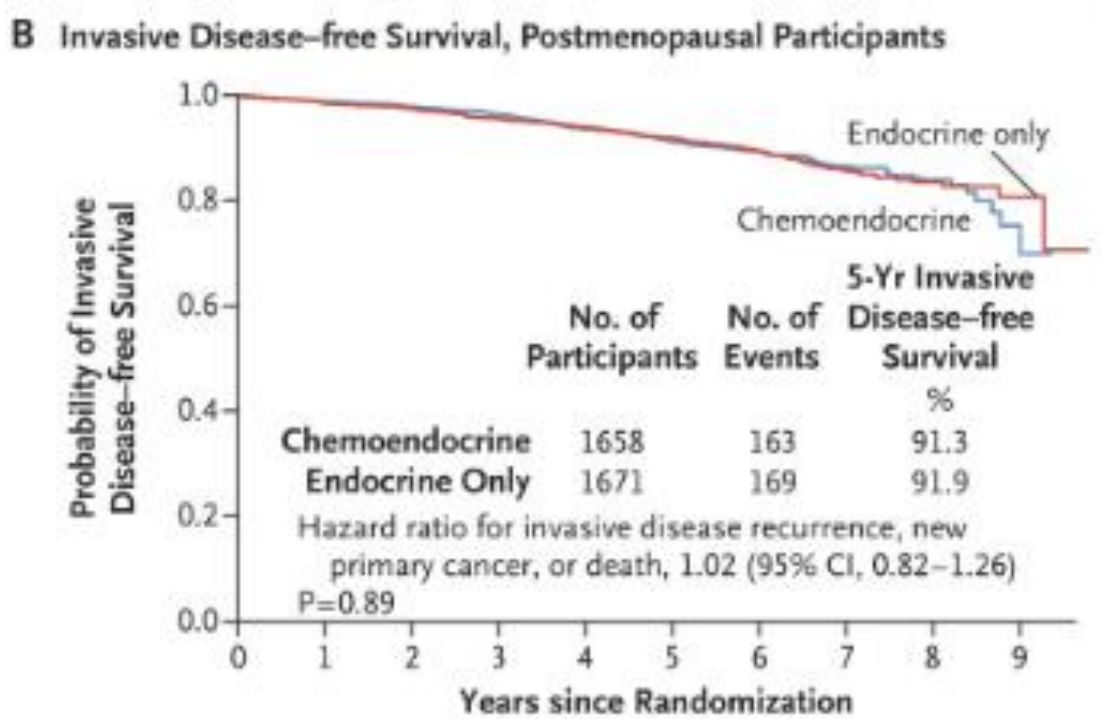


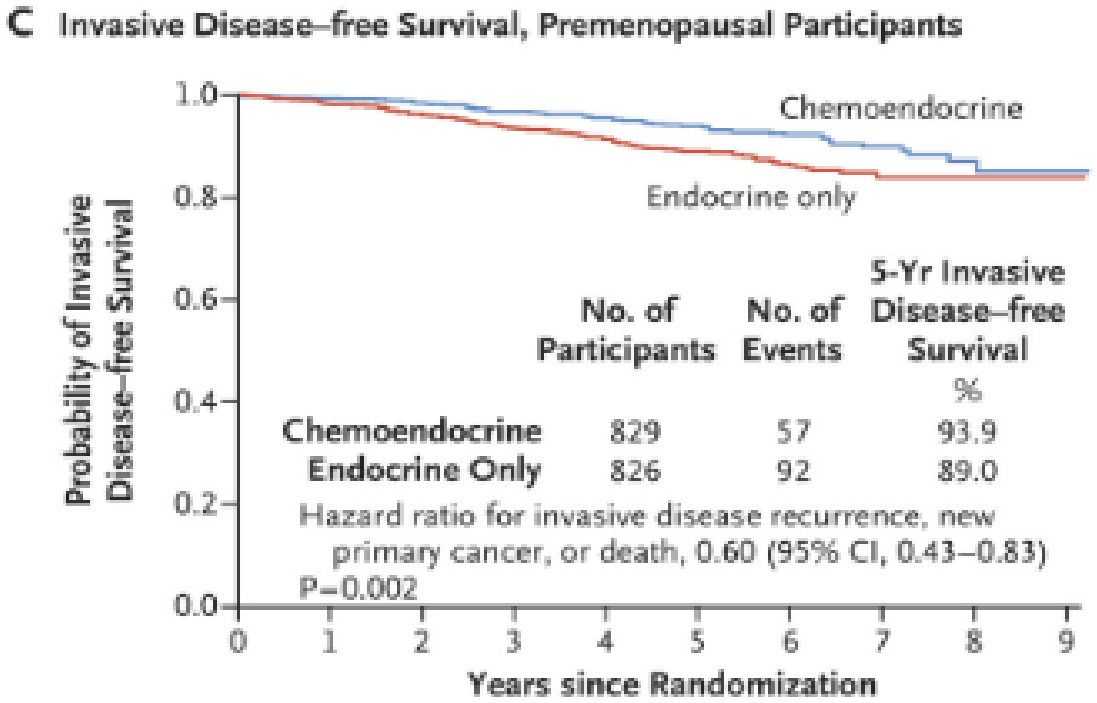


N Engl J Med 2018;379:111-21.

RxSponder

- Designed to evaluate recurrence score (0-25) in women with HR+/HER2-, node positive (1-3 nodes) breast cancer
- Randomized to endocrine therapy along versus chemotherapy followed by endocrine therapy

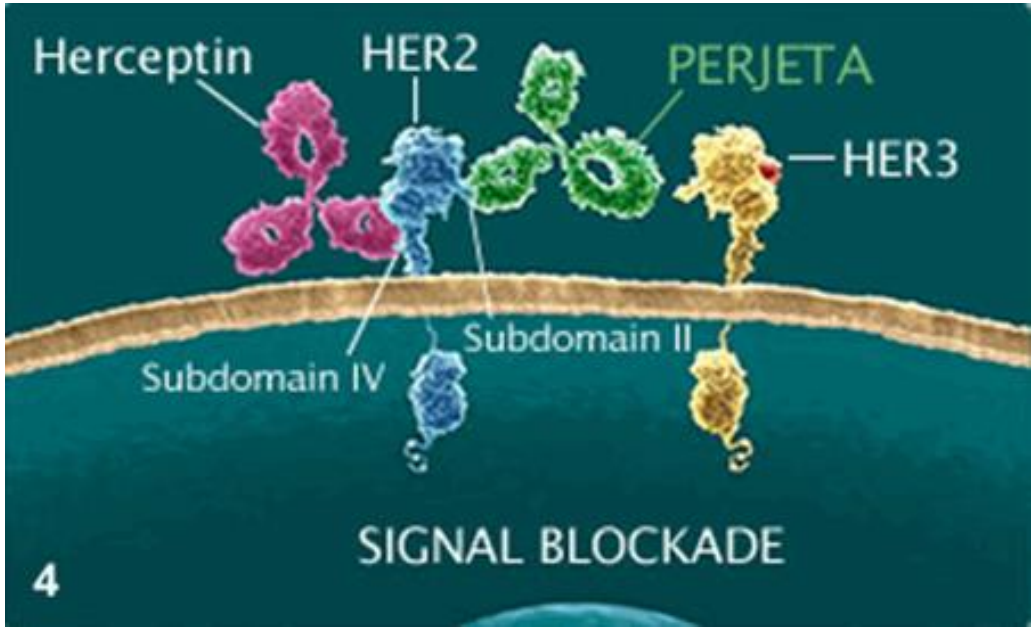


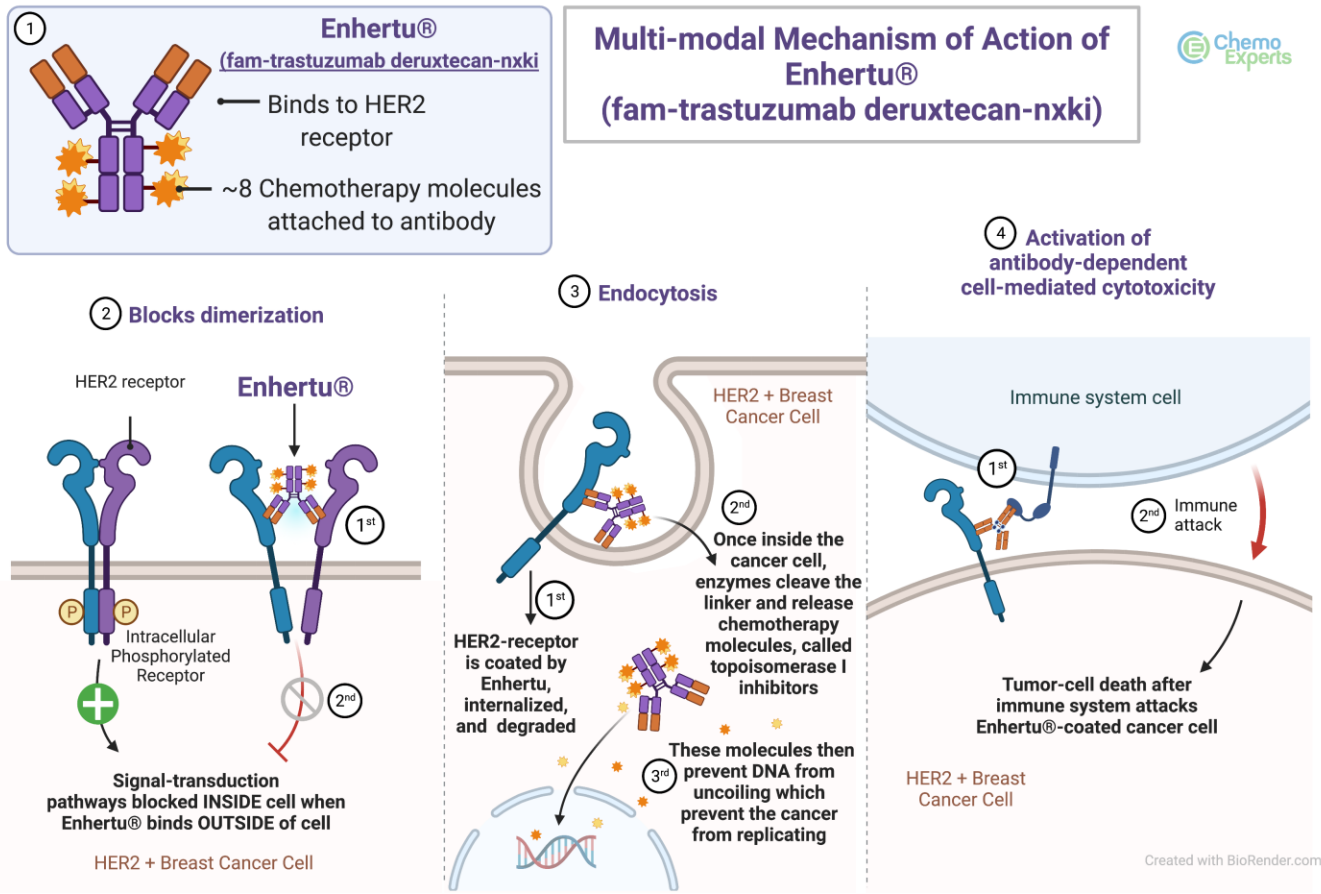


N Engl J Med 2021; 385: 2336-2347

Targeted Therapy

- Trastuzumab – Humanized monoclonal antibody, binds to extracellular HER2 subdomain IV
- Pertuzumab – Humanized monoclonal antibody, binds to extracellular HER2 subdomain II and blocks dimerization





The NEW ENGLAND JOURNAL of MEDICINE

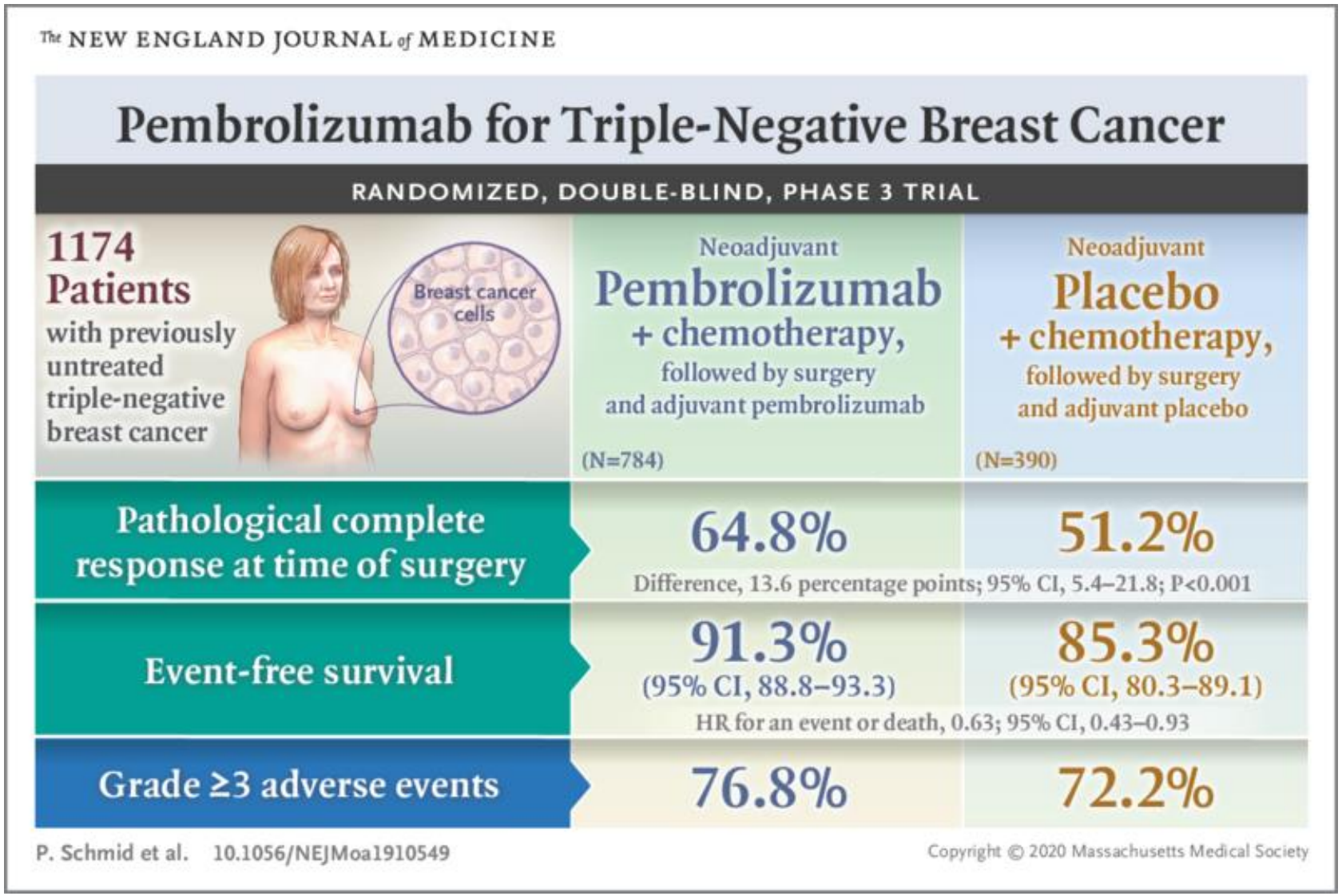
ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

- Early studies suggested that only HER2+ pts (IHC 3+ or FISH+) would respond to targeted treatment
- DESTINY-Breast04 (Phase III trial): Patient with metastatic BC with HER2 low disease (IHC 1+ or IHC2+ AND FISH neg) and previous chemotherapy
- Randomized 2:1 to Enhertu (Trastuzumab liked to deruxtecan) or MD choice
- Improved PFS (9.9 mo vs 5.1 mo, HR 0.5, $p<0.001$) and OS (23.4 mo vs 16.8 mo, HR 0.64, $p=0.001$)

N Engl J Med 2022; 387:9-20.

Immunotherapy – KEYNOTE 522 study



Timing of chemotherapy

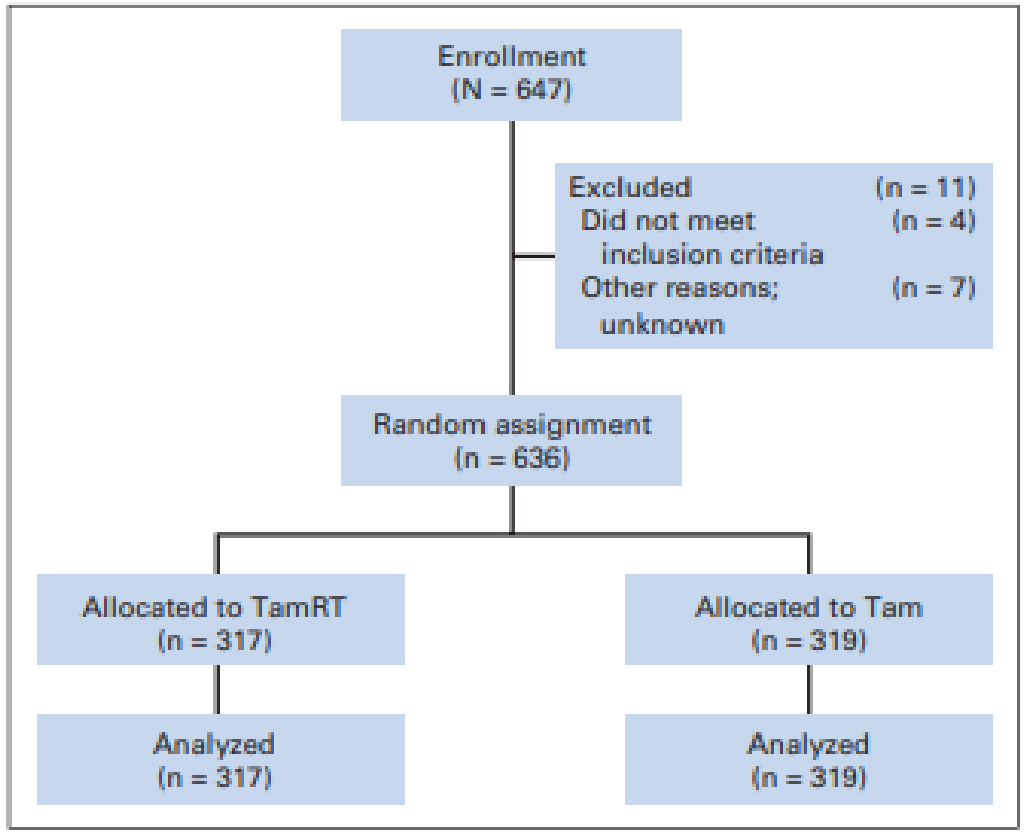
- Advantages of neoadjuvant therapy
  - Helps to downstage unresectable primary to an operable state
  - Reduces the need for mastectomies
  - Reduces the need for axillary lymph node dissections
  - Allows early treatment of potential micrometastatic disease
  - Offers real time prognostic information based on pathologic response rates (TNBC and HER2 positive disease)
  - Unclear overall survival benefit when compared to adjuvant therapy

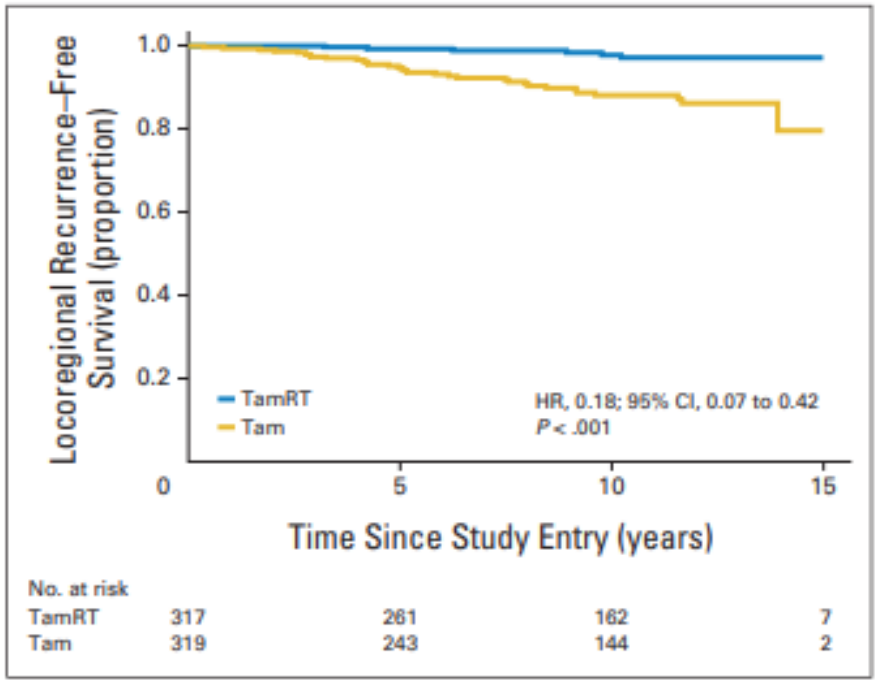
Radiation Therapy

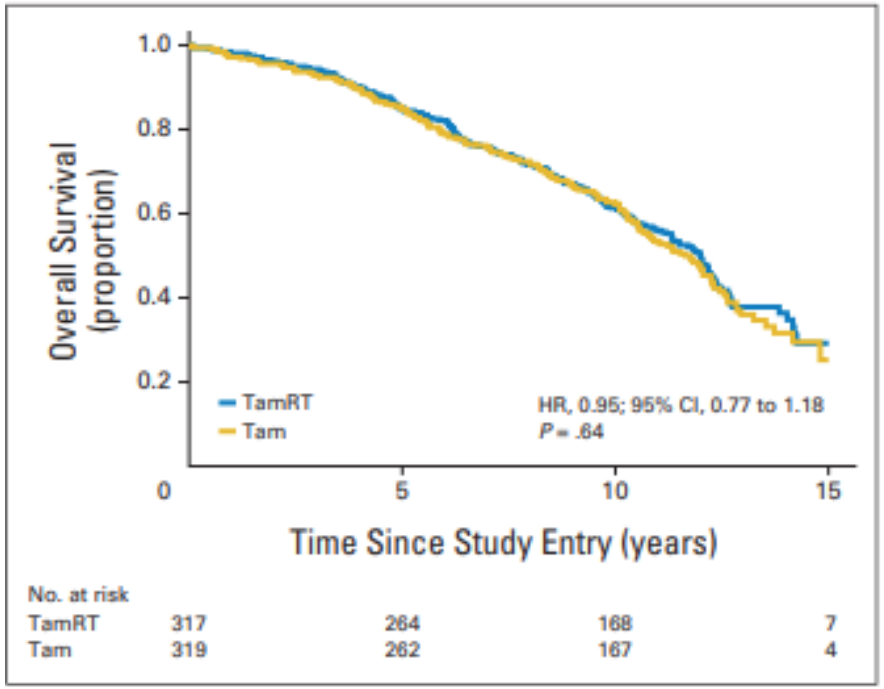
- CALGB 9343
- PRIME II
- FAST-FORWARD

Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343

Kevin S. Hughes, Lauren A. Schnaper, Jennifer R. Bellon, Constance T. Cirrincione, Donald A. Berry, Beryl McCormick, Hyman B. Muss, Barbara L. Smith, Clifford A. Hudis, Eric P. Winer, and William C. Wood





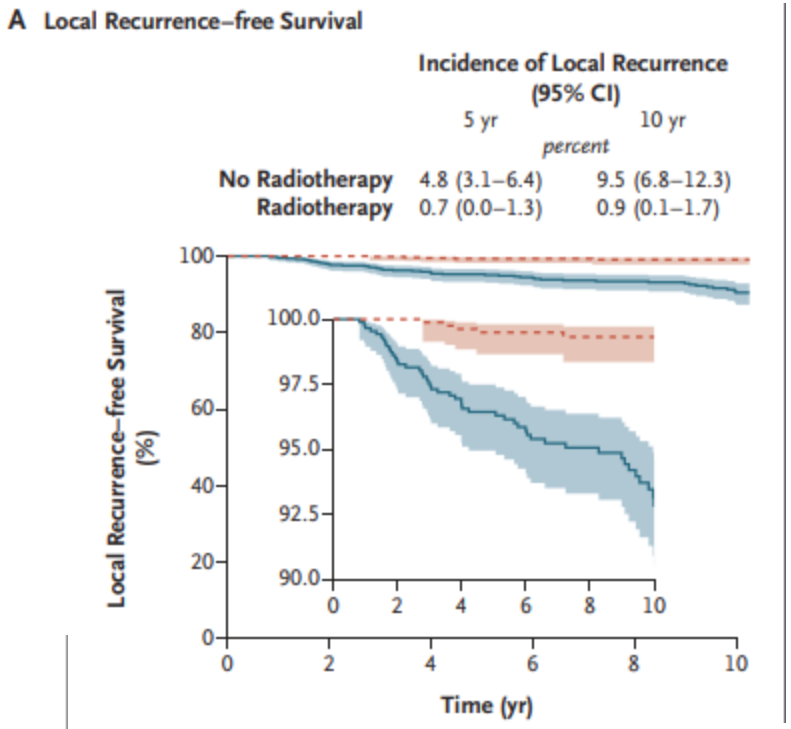


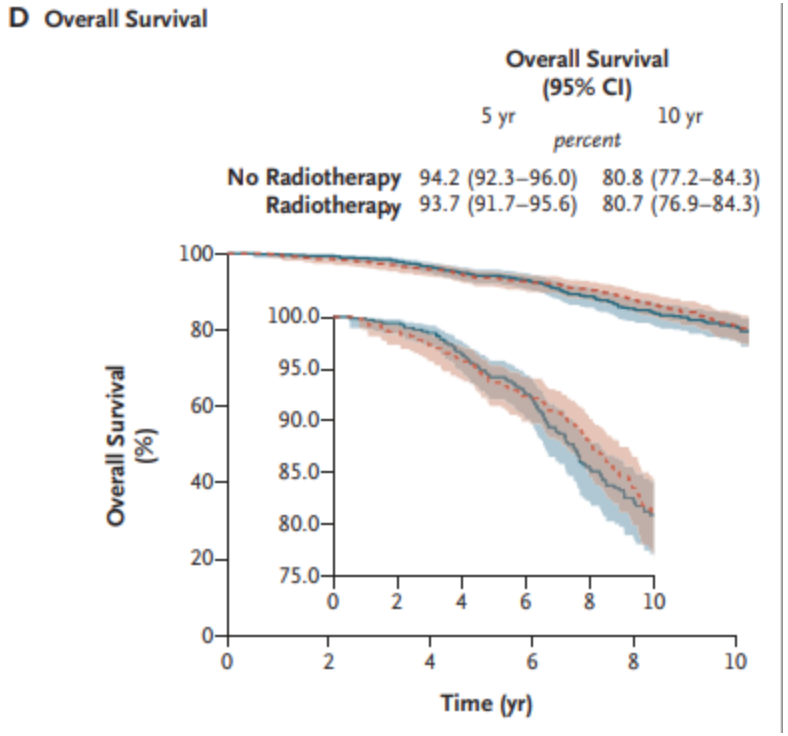
J Clin Oncol 2013; 31(19): 2382-2387.

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Ian H. Kunkler, M.B., B.Chir., Linda J. Williams, Ph.D., Wilma J.L. Jack, M.B., Ch.B., David A. Cameron, M.D., and J. Michael Dixon, M.D.

- 2003-2009: Women aged 65+ with HR+, node negative breast cancer, size ≤ 3cm, treated with BCS and adjuvant endocrine therapy
- Randomized to adjuvant RT or no RT



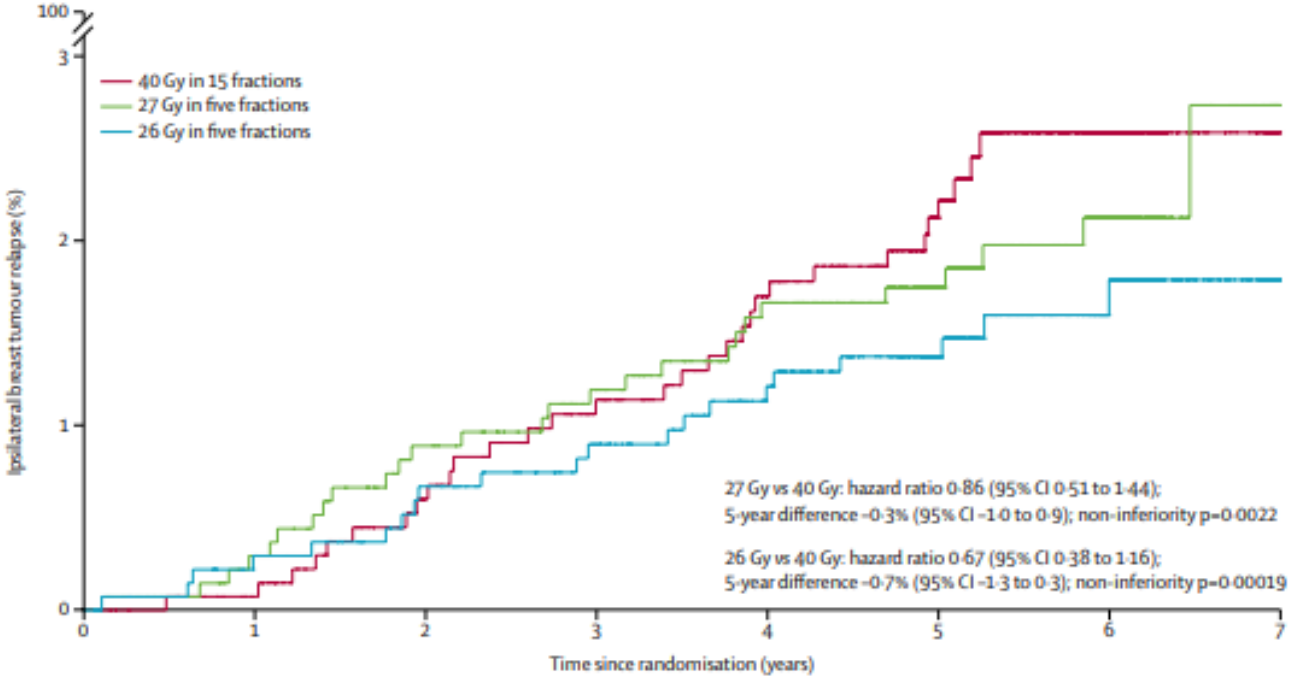


N Eng J Med 2023; 388(7):585-594.

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

- 2011-2014: Randomized pts with pT1-3, pN0, M0 BC after BCS or mastectomy to 40 Gy/15 fr, 27Gy/5 fr, or 26 Gy/5 fr
- Primary end point – ipsilateral breast tumor relapse
- Non-inferiority trial (Assume 2% 5yr recurrence for standard 40Gy)



Lancet 2020; 23:1613-1626

What happens after…

Survivorship – General Principles

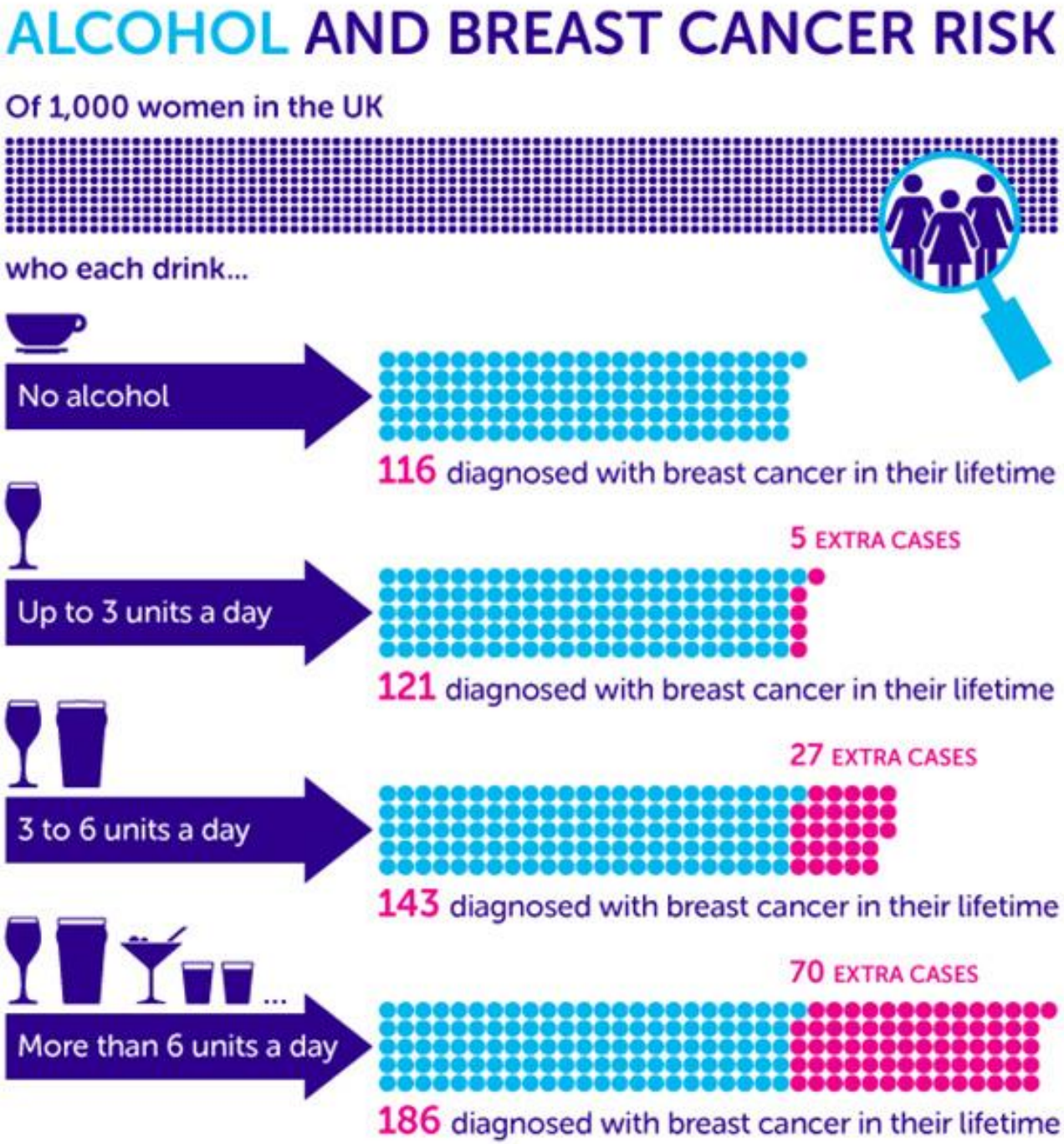
- Surveillance for spread/recurrence and screen for subsequent primary cancers
- Monitor long-term effects of cancer
- Prevent and detect late effects of cancer and therapy
- Coordinate care between primary care and specialists to ensure all health needs met
- Plan for ongoing survivorship care

Cancer Screening

- Overall cancer rate in survivors is higher than in general population.
- Screening
  - Colon cancer
  - Cervical cancer
  - Lung cancer
- For those living with metastatic disease, recommendations are tailored to individual risk and disease status
- Screening for treatment-related subsequent primary cancers
  - Tamoxifen – Increased risk of endometrial cancer, mainly in postmenopausal women; Assess vaginal pain or bleeding annually
  - PARP Inhibitors – Increased risk of MDS & AML; Rare and usually after long-term treatment
  - Mantel/Chest radiation – Increased risk of angiosarcoma

Lifestyle changes

- Smoking cessation
- Wear sunscreen
- Limiting alcohol
- Good sleep hygiene
- Maintain healthy weight
- Exercise



https://news.cancerresearchuk.org/

Lifestyle changes

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Effects of Exercise on Health-Related Outcomes in Those with Cancer

What can exercise do?

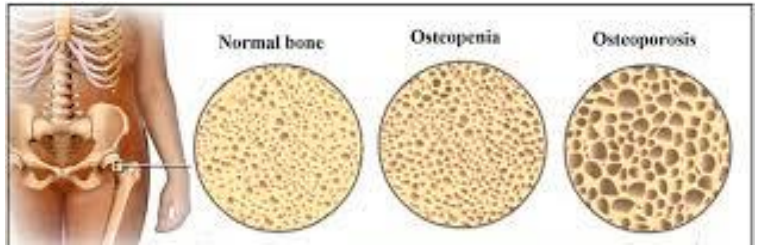
- **Prevention of 7 common cancers***
  Dose: 2018 Physical Activity Guidelines for Americans: 150-300 min/week moderate or 75-150 min/week vigorous aerobic exercise
- **Survival of 3 common cancers****
  Dose: Exact dose of physical activity needed to reduce cancer-specific or all-cause mortality is not yet known; Overall more activity appears to lead to better risk reduction

**bladder, breast, colon, endometrial, esophageal, kidney and stomach cancers*
***breast, colon and prostate cancers*

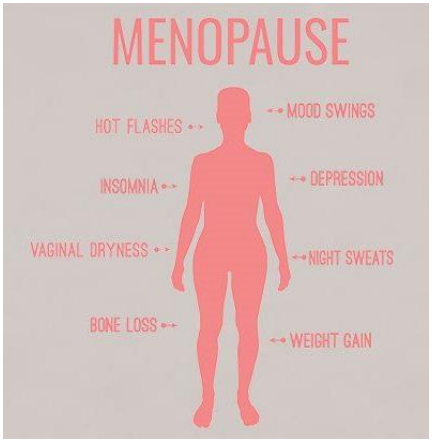
Overall, avoid inactivity, and to improve general health, aim to achieve the current physical activity guidelines for health (150 min/week aerobic exercise and 2x/week strength training).

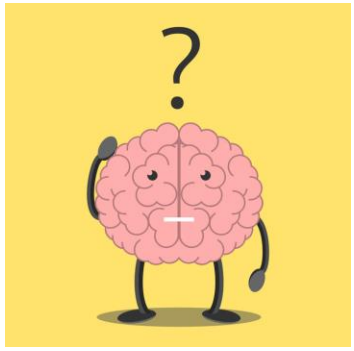
Outcome	Aerobic Only	Resistance Only	Combination (Aerobic + Resistance)
Strong Evidence	Dose	Dose	Dose
Cancer-related fatigue	**3x**/week for **30** min per session of moderate intensity	**2x**/week of **2** sets of **12-15** reps for major muscle groups at moderate intensity	**3x**/week for **30** min per session of moderate aerobic exercise, plus **2x**/week of resistance training **2** sets of **12-15** reps for major muscle groups at moderate intensity
Health-related quality of life	**2-3x**/week for **30-60** min per session of moderate to vigorous	**2x**/week of **2** sets of **8-15** reps for major muscle groups at a moderate to vigorous intensity	**2-3x**/week for **20-30** min per session of moderate aerobic exercise plus **2x**/week of resistance training **2** sets of **8-15** reps for major muscle groups at moderate to vigorous intensity
Physical Function	**3x**/week for **30-60** min per session of moderate to vigorous	**2-3x**/week of **2** sets of **8-12** reps for major muscle groups at moderate to vigorous intensity	**3x**/week for **20-40** min per session of moderate to vigorous aerobic exercise, plus **2-3x**/week of resistance training **2** sets of **8-12** reps for major muscle group at moderate to vigorous intensity
Anxiety	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Depression	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Lymphedema	Insufficient evidence	**2-3x**/week of progressive, supervised, program for major muscle groups does not exacerbate lymphedema	Insufficient evidence
Moderate Evidence			
Bone health	Insufficient evidence	**2-3x**/week of moderate to vigorous resistance training plus high impact training (sufficient to generate ground reaction force of **3-4** time body weight) for at least **12** months	Insufficient evidence
Sleep	**3-4x**/week for **30-40** min per session of moderate intensity	Insufficient evidence	Insufficient evidence

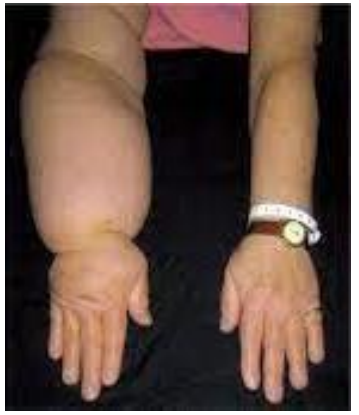
Citation: bit.ly/cancer_exercise_guidelines



Long-Term Effects





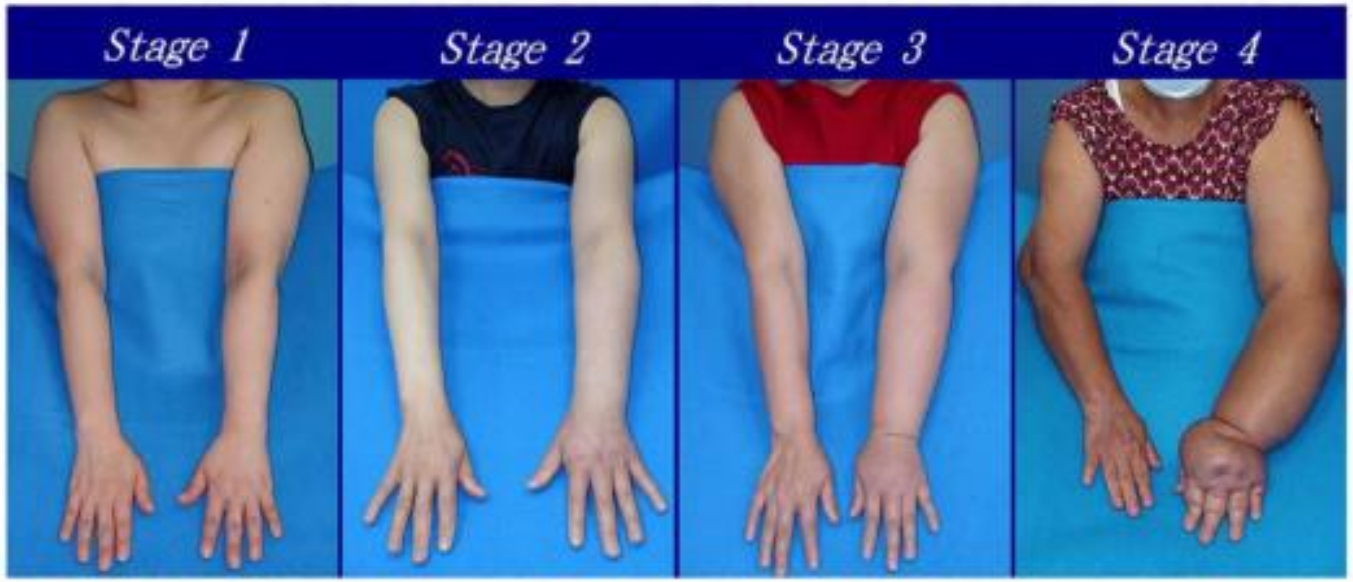


Cardiovascular Disease

- Cancer treatment can result in cardiovascular disease
  - Anthracycline based chemotherapy
  - Trastuzumab
  - Radiation therapy
- Cardiovascular disease is a leading cause of death in cancer survivors
  - Need to also address co-morbidities
- Cardio-oncology

Lymphedema

- Can affect breast/chest wall or arms
- Prevention
- Risk
- Treatment
  - Compression therapy
  - Pumps
  - Surgical therapy



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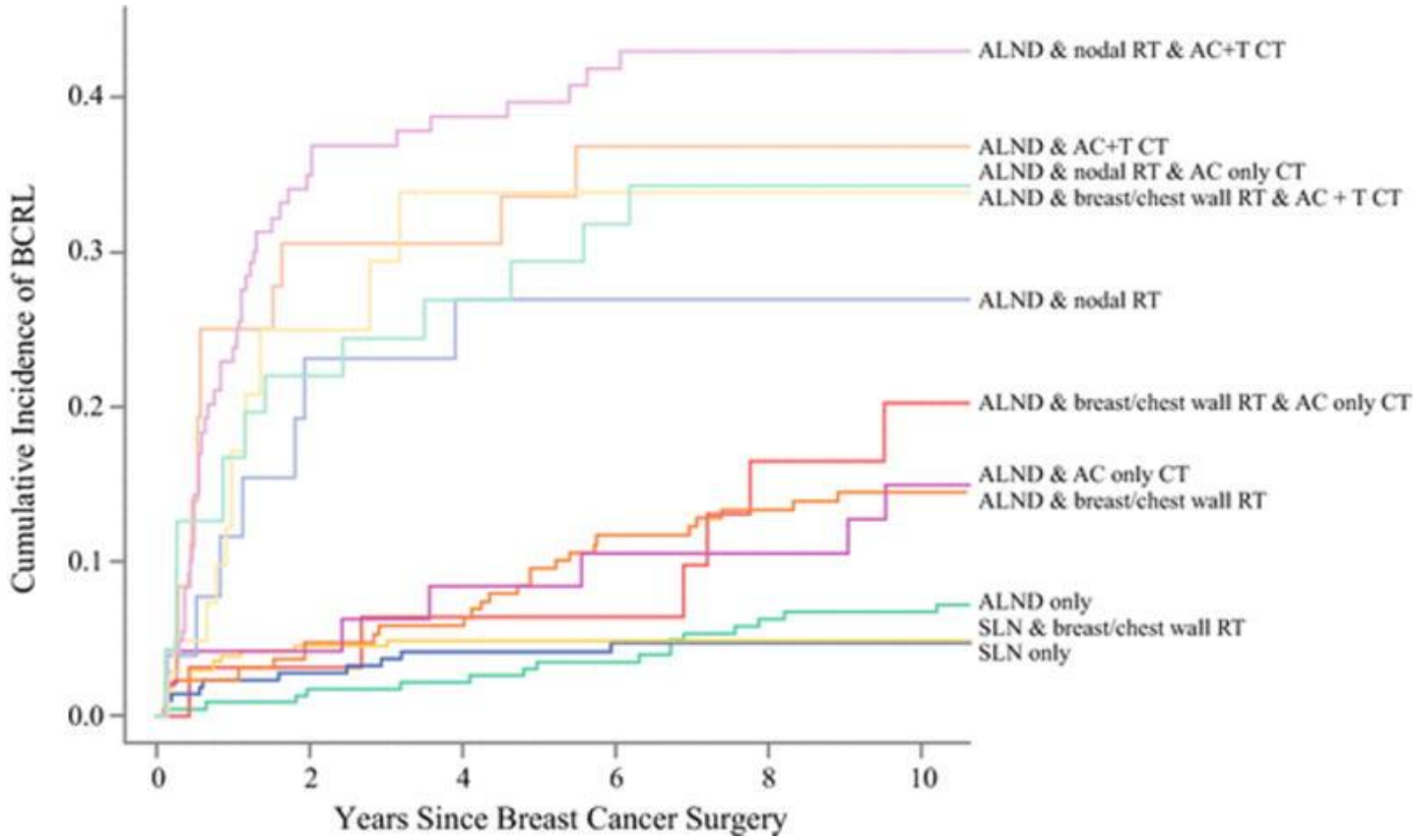

Nguyen TT et al, Ann Surg Oncol. 2017;24(10):2972-2980

Risk factors for breast cancer–related lymphedema in patients undergoing 3 years of prospective surveillance with intervention

Louise A. Koelmeyer, PhD, OT [1]; Katrina Gaitatzis, Grad Dip(Psych)[1]; Mary S. Dietrich, PhD, MS[2]; Chirag S. Shah, MD [3]; John Boyages, MD, PhD[1,4]; Sarah A. McLaughlin, MD[5]; Bret Taback, MD[6]; Deonni P. Stolldorf, PhD, RN[2]; Elisabeth Elder, MD, PhD[7,8,9]; T. Michael Hughes, MD[10]; James R. French, MD[7,8,9]; Nicholas Ngui, MD[11]; Jeremy M. Hsu, MD[7,9,12]; Andrew Moore, MD[13]; and Sheila H. Ridner, PhD, RN [2]

- Factors associated WITH:
  - ALND ($p<0.001$)
  - Taxane based chemotherapy ($p<0.001$)
  - Regional nodal XRT ($p\leq0.001$)
  - BMI > 30 ($p=0.002$)
  - Rurality ($p=0.037$
- Factors NOT associated with:
  - Mastectomy
  - Age
  - HTN
  - DM
  - Smoking
  - Seroma
  - Air travel

Cancer 2022; 128:3408-3415.

Lymphedema

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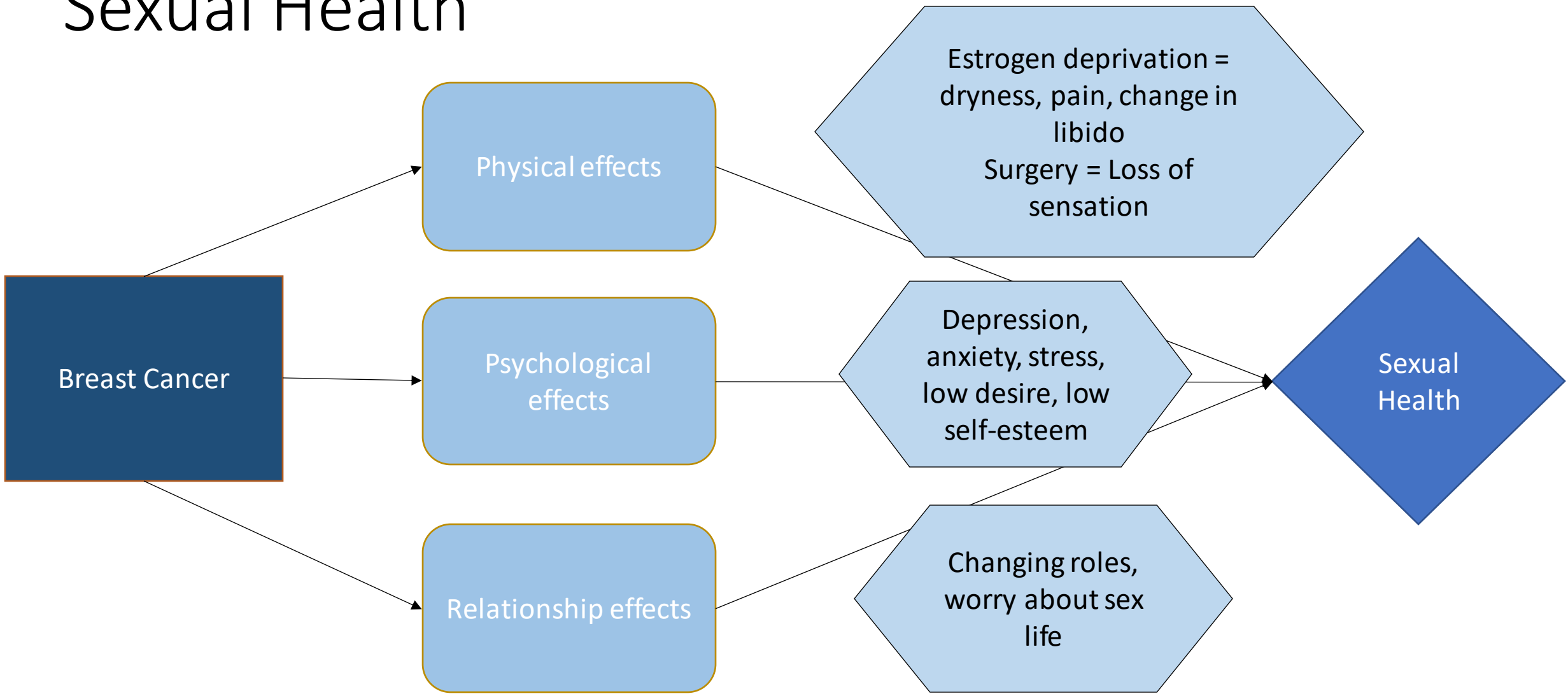
Hormonal Therapy Symptoms

- Tamoxifen
  - Menopausal symptoms
  - Depression
  - Thromboembolism
  - Endometrial carcinoma
- Aromatase Inhibitors
  - Osteoporosis/osteopenia

Sexual Health



New Frontiers

…Breast Cancer in 2033