Breast Cancer Management in the Modern Era: Improving Outcomes and Increasing Complexities

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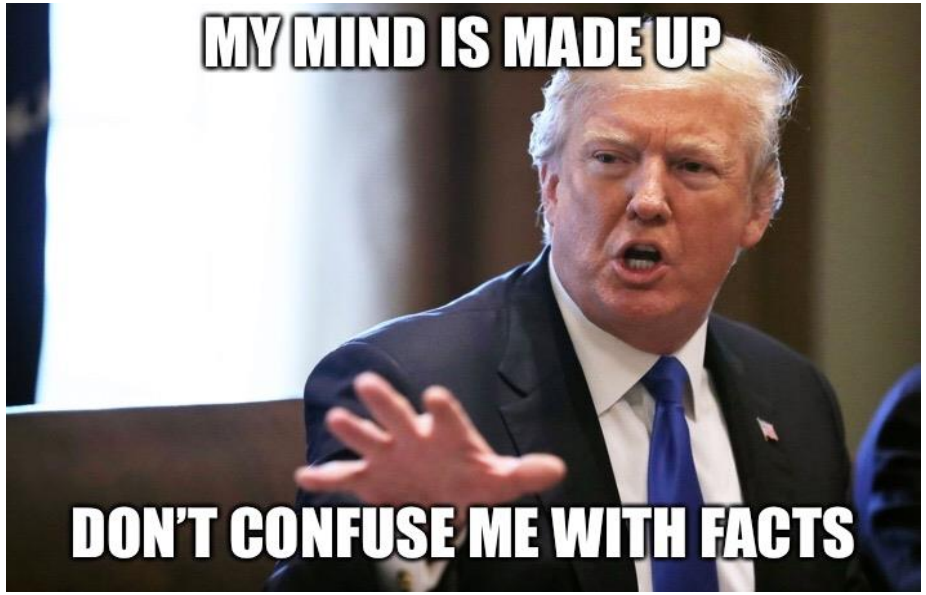
Disclosures

- Aptitude Health
- NAPBC – site reviewer

Quick Facts on Breast Cancer

- Every 2 minutes in the U.S. - a woman is diagnosed with breast cancer.
- In 2022, over 280,000 women will be diagnosed with invasive breast cancer and over 60,000 women will be diagnosed with non-invasive breast cancer (DCIS)
- Every 13 minutes, a woman dies of breast cancer.
- About 2,800 **MEN** are expected to be diagnosed with the disease.



Past vs. Present

- In the 1970s, only 1 in 11 women were diagnosed with breast cancer.
- In 2022, it's 1 in 8 (more women are getting breast cancer)
- **Why?**

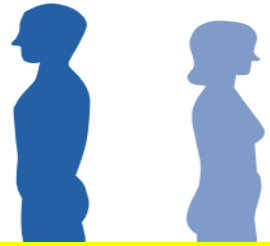
-Living longer
-Obesity
-Less childbearing
-Older age at firstborn child
-Hormonal therapy use
-Better detection methods

Can we cure breast cancer?

10 leading cancers in the US

ed New Cases

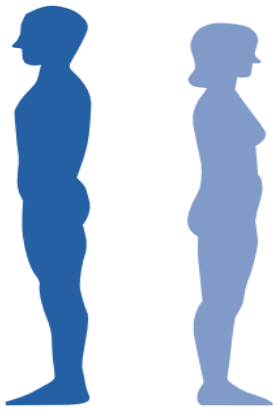
Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%



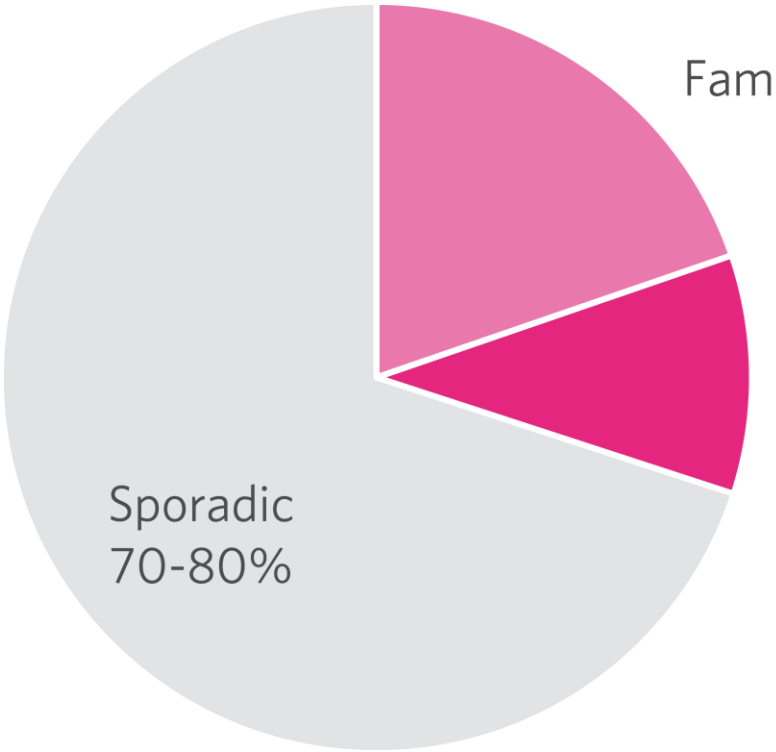
We can cure 85% of all breast cancers

Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**

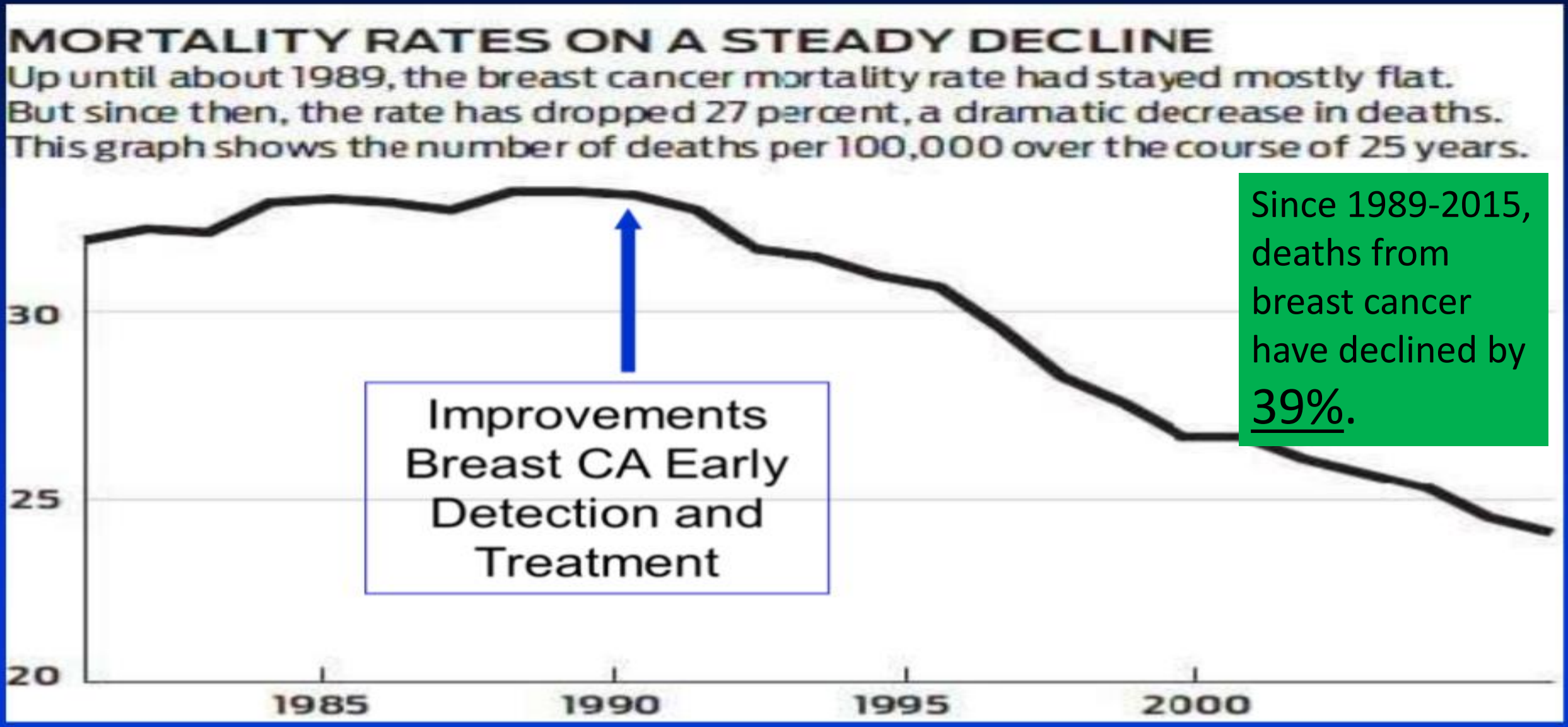


What about family history?



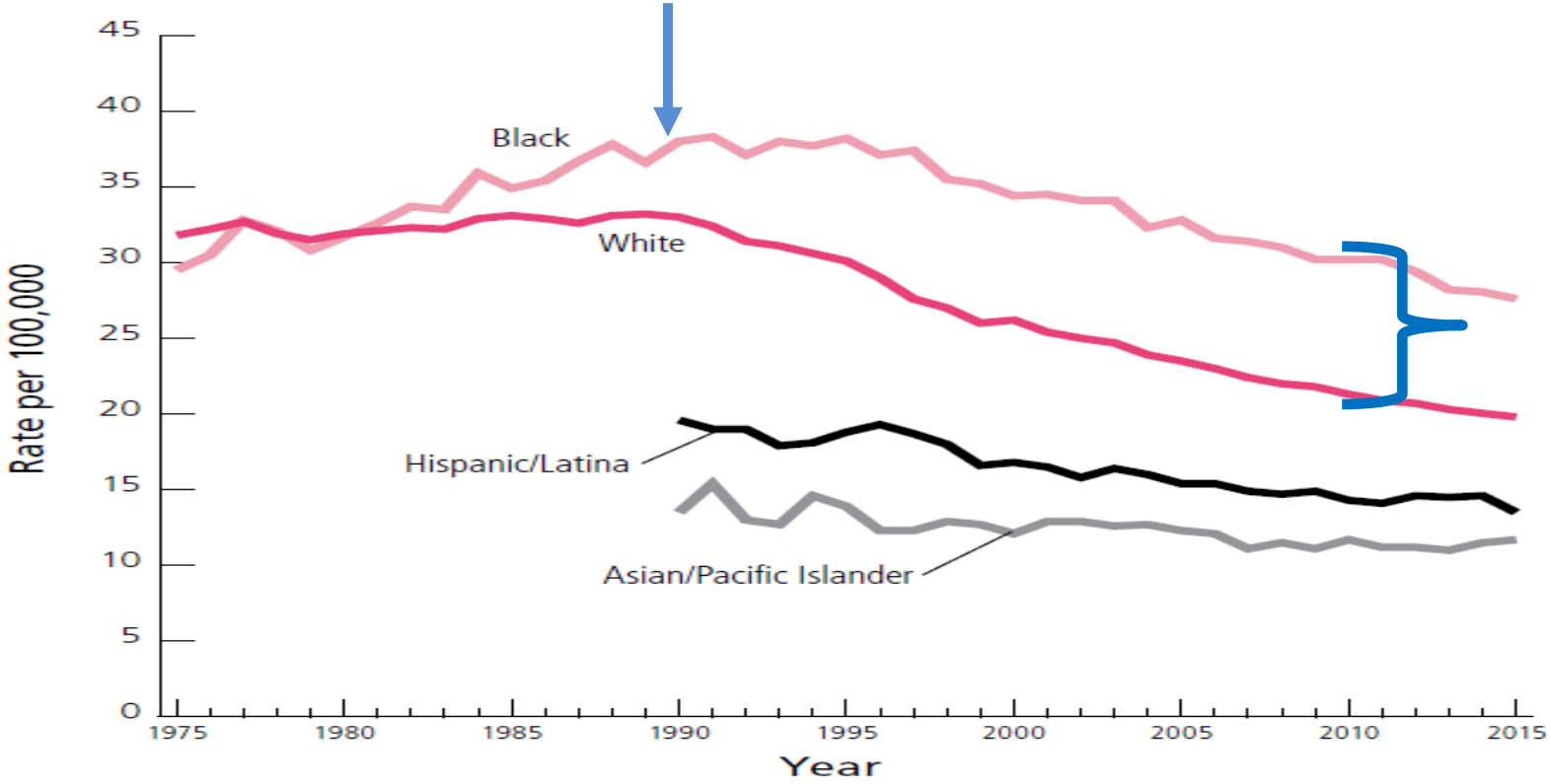
BRCA1 and BRCA2 are the most common causes of hereditary breast and hereditary ovarian cancer

Good News: Overall Declining Breast Cancer Mortality Rates!



Mortality has decreased over time

Figure 6b. Trends in Female Breast Cancer Death Rates by Race/Ethnicity, 1975-2015, US



White women have benefited most from lower death rates

National Center for Health Statistics, Centers for Disease Control and Prevention, 2017.

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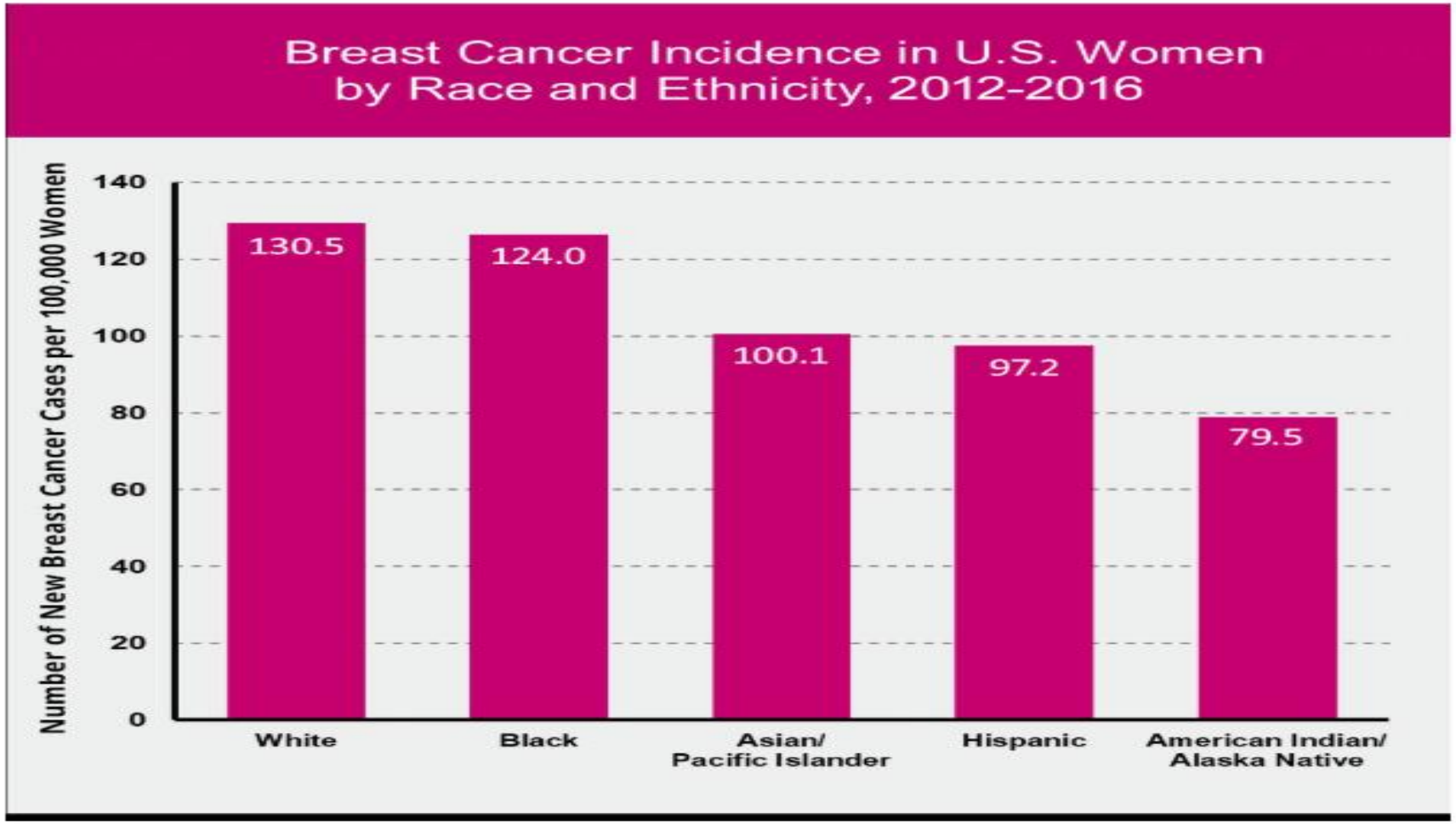
Disparities in Breast Cancer

- Affects white American women more often than African American women.



SEER Cancer Statistics Review, 1975-2016

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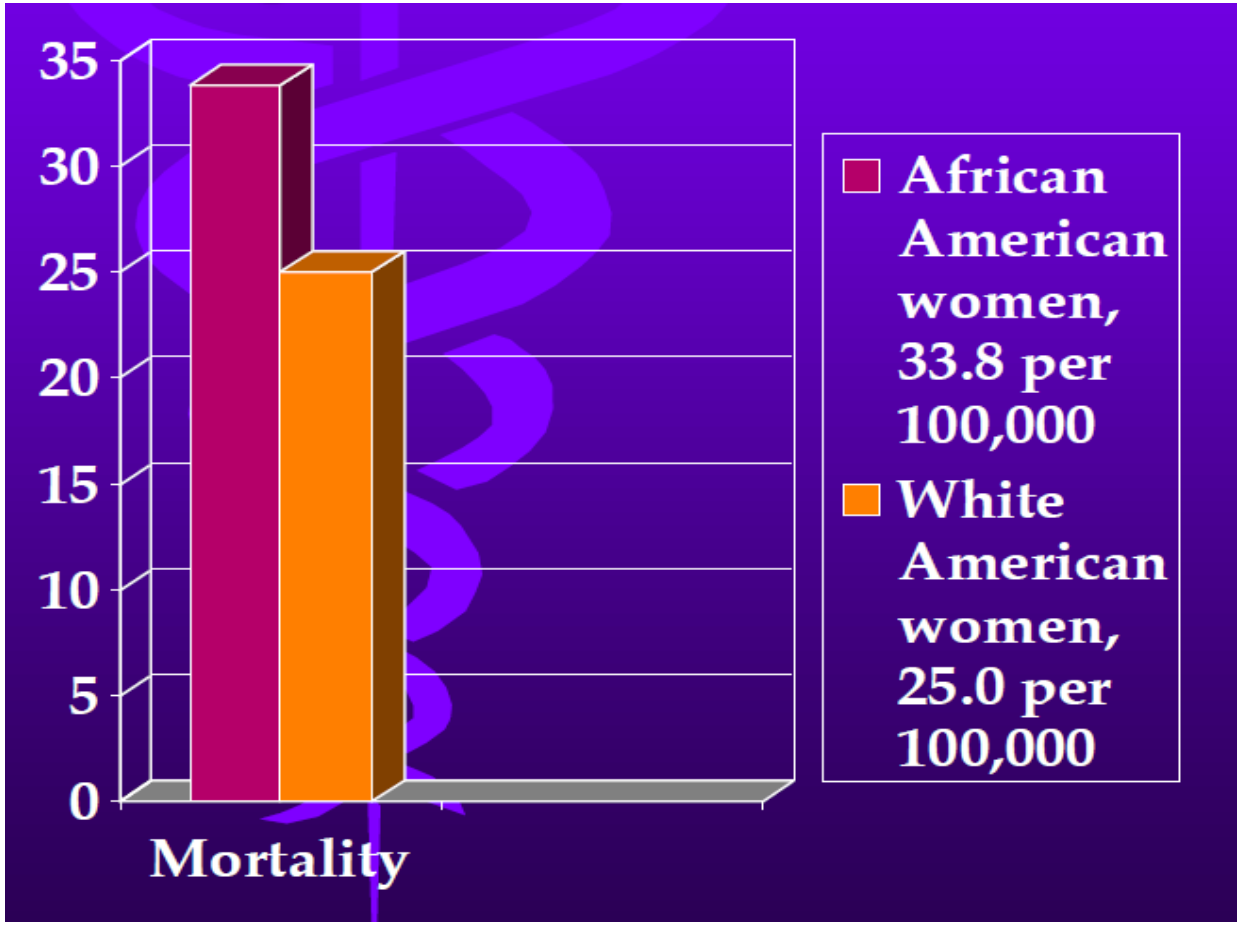
Disparities in Breast Cancer

Race and ethnicity	Lifetime risk of breast cancer
White	13%
Black	12%
Asian/Pacific Islander	11%
Hispanic	10%
American Indian/Alaska Native	8%

http://seer.cancer.gov/csr/1975_2016/

Disparities in Breast Cancer

- The death rate for African American women is much higher than that of White American.



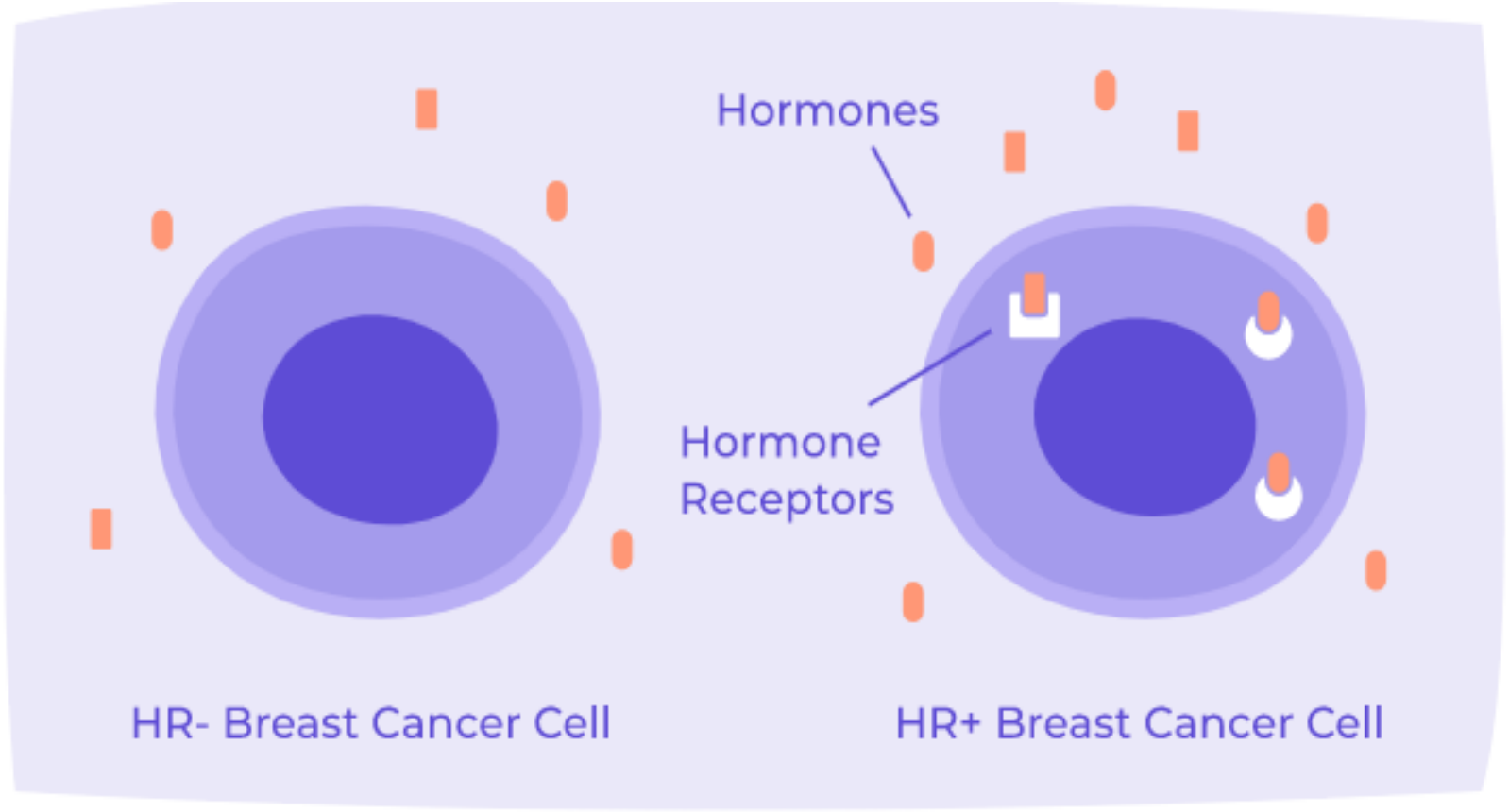
http://www.omhrc.gov/templates/content.aspx?ID=2826

Burden of Cancer in AA Women vs. White Women

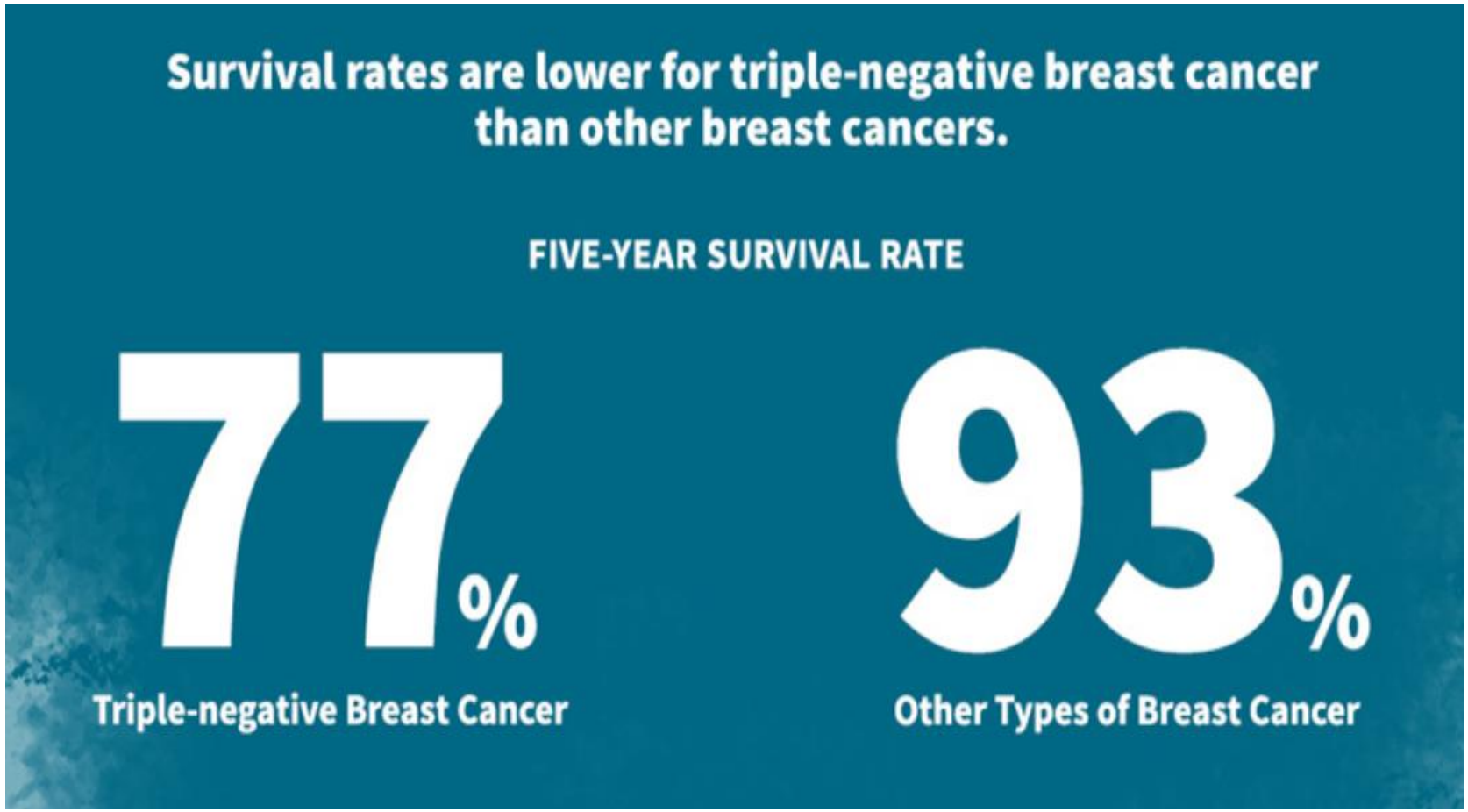
- Higher mortality rate
- More advanced stage distribution
- Younger age distribution (40% AA pts <50 years old vs. 20% white pts <50 years old)
- Increased risk of bad tumor features
- Higher incidence of male breast cancer

- Socioeconomic Disparities
- Tumor biology
- Genetics
- Lifestyle & Reproductive Experiences
- Environmental exposures
- Diet/Nutrition

Different Types of Breast Cancer

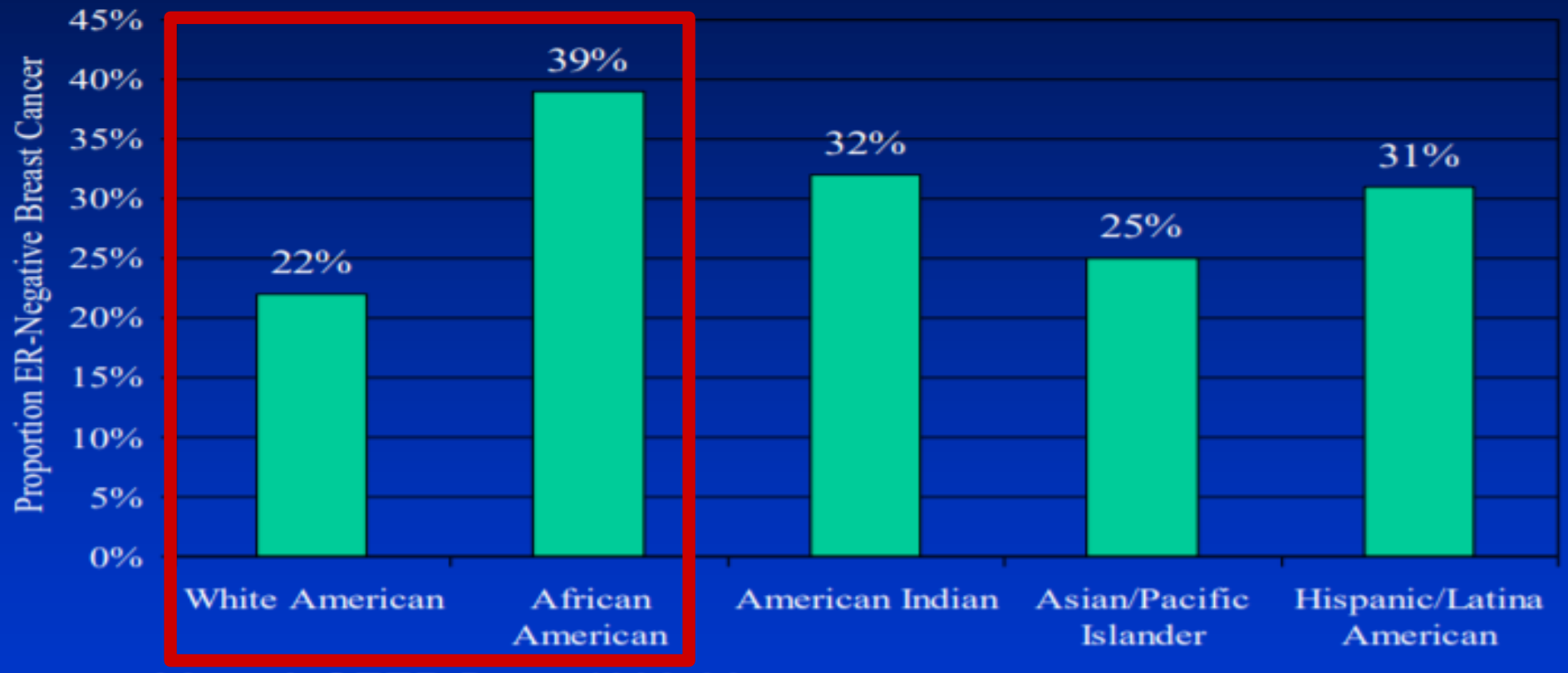


Triple negative breast cancer



- More likely to spread
- More likely to recur
- Requires chemotherapy
- Fewer treatment options

Disparities in Breast Tumor Biology: ER-Negative Breast Cancer in the U.S.



Li et al; SEER Data, 1992-98
Arch Int Med 2003

Do Women Obtain their Mammograms?

	Percentage of women 40 and older who had a mammogram in the past 2 years in 2015 (most recent data available)
Black	69%
White	65%
Hispanic	61%
American Indian/Alaska Native	60%
Asian	59%

https://ww5.komen.org/BreastCancer

Delays to follow-up care

- Some findings have shown Black/African-American women may have more delays in follow-up after an abnormal mammogram than white women.

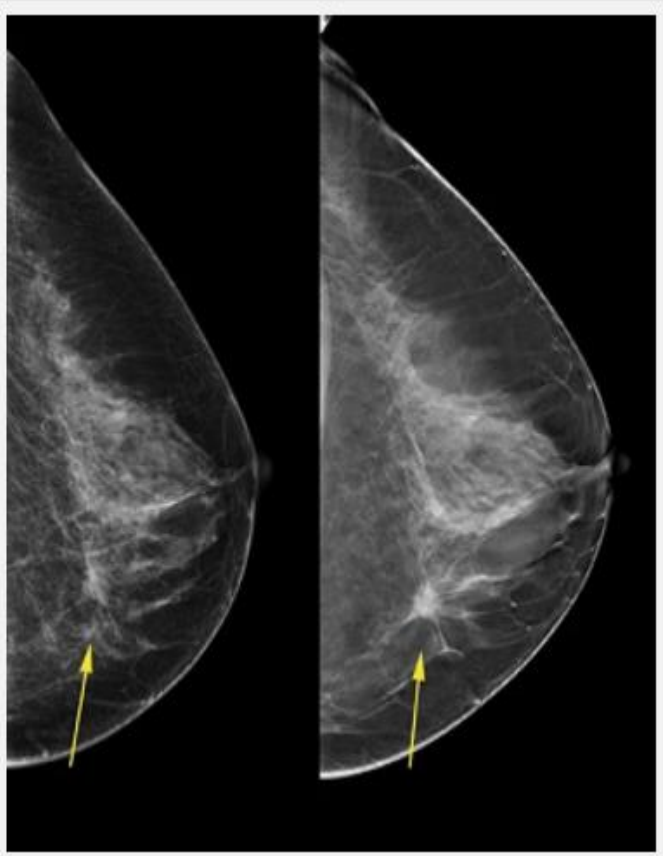
- Longer delays = worse outcomes

▲ *Treatment types for breast cancer.*

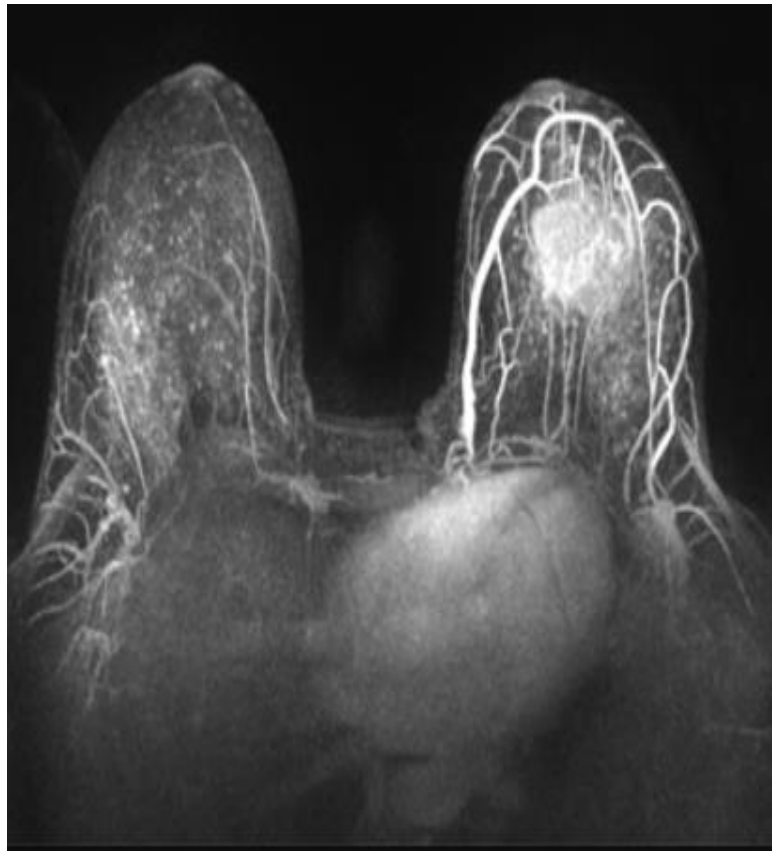
DeSantis CE et al. Cancer statistics for African Americans, 2019. CA Cancer J Clin 2019.

Why has mortality decreased?

- Improved screening/surveillance – earlier detection
- Use of digital 2D and 3D mammograms
- Rising rates of mammogram screening



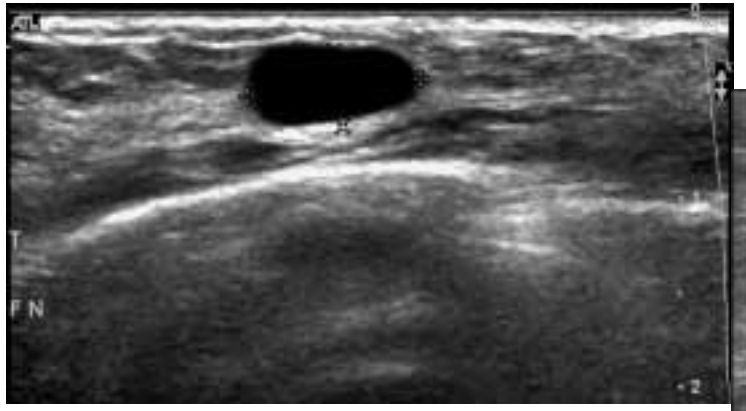
2D vs. 3D mammogram

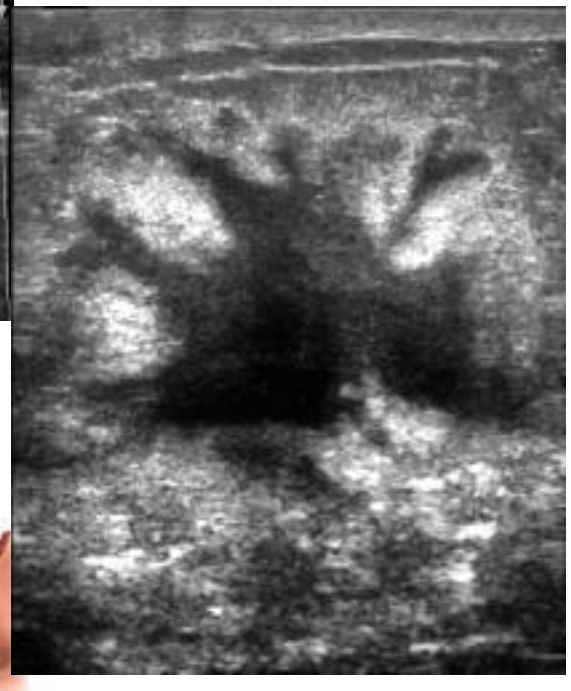


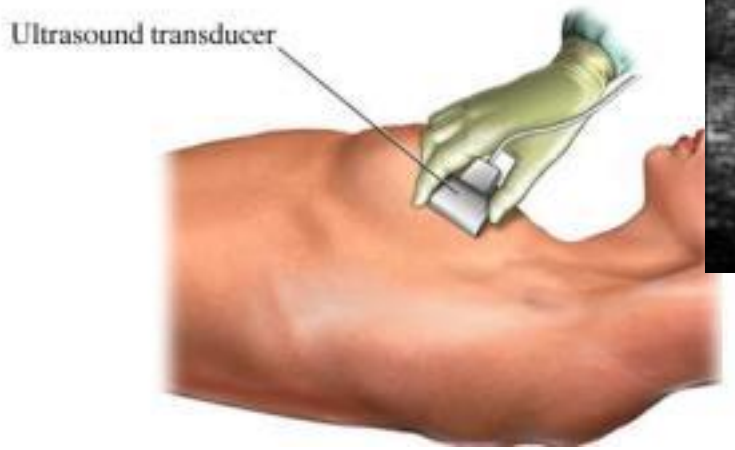
MRI

Breast Ultrasound

- No radiation
- Solid versus cystic structures
- Noninvasive

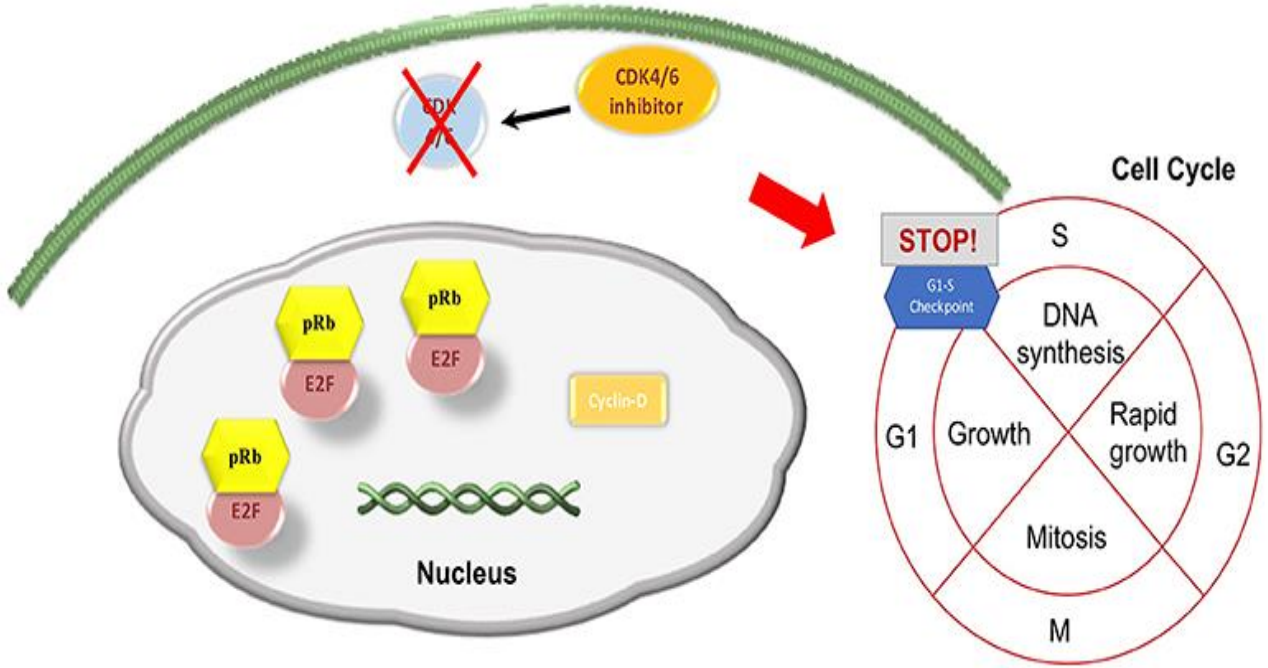


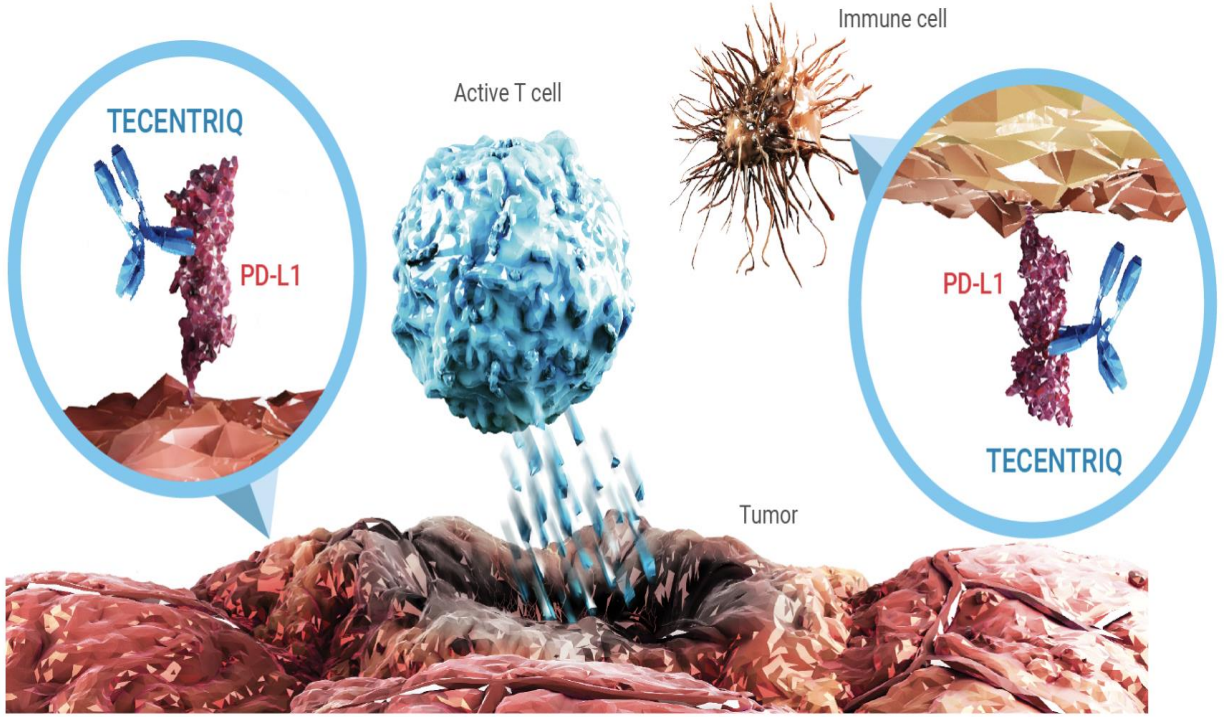


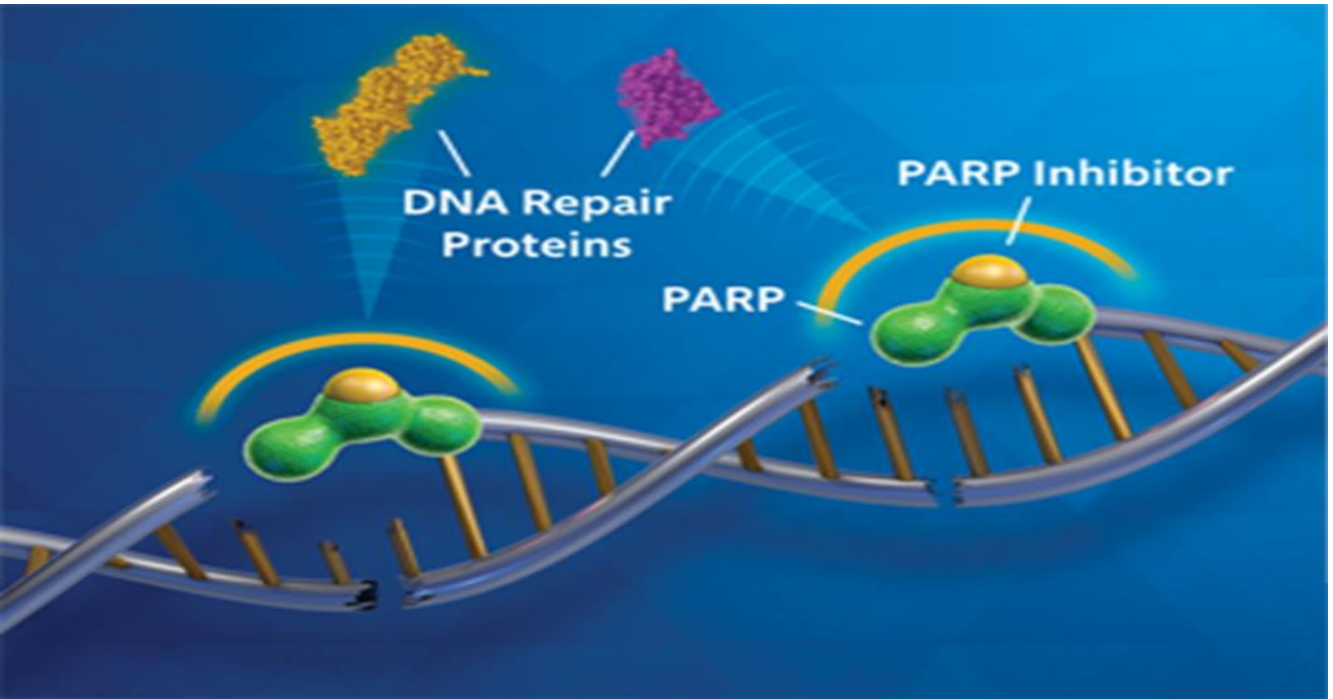


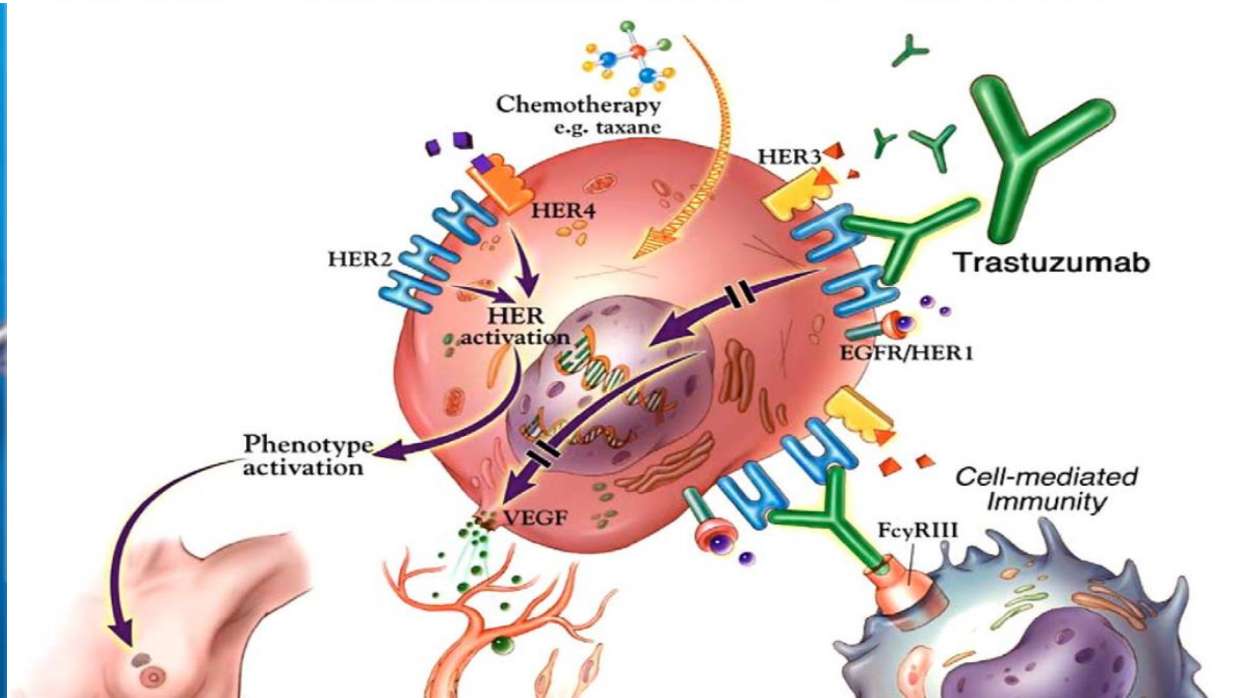
Why has mortality decreased?

- Improved systemic treatments
  - Advanced 2nd and 3rd generation chemotherapy regimens
  - Targeted treatment (smart drugs)
  - Immunotherapy (uses your own body's immune system)

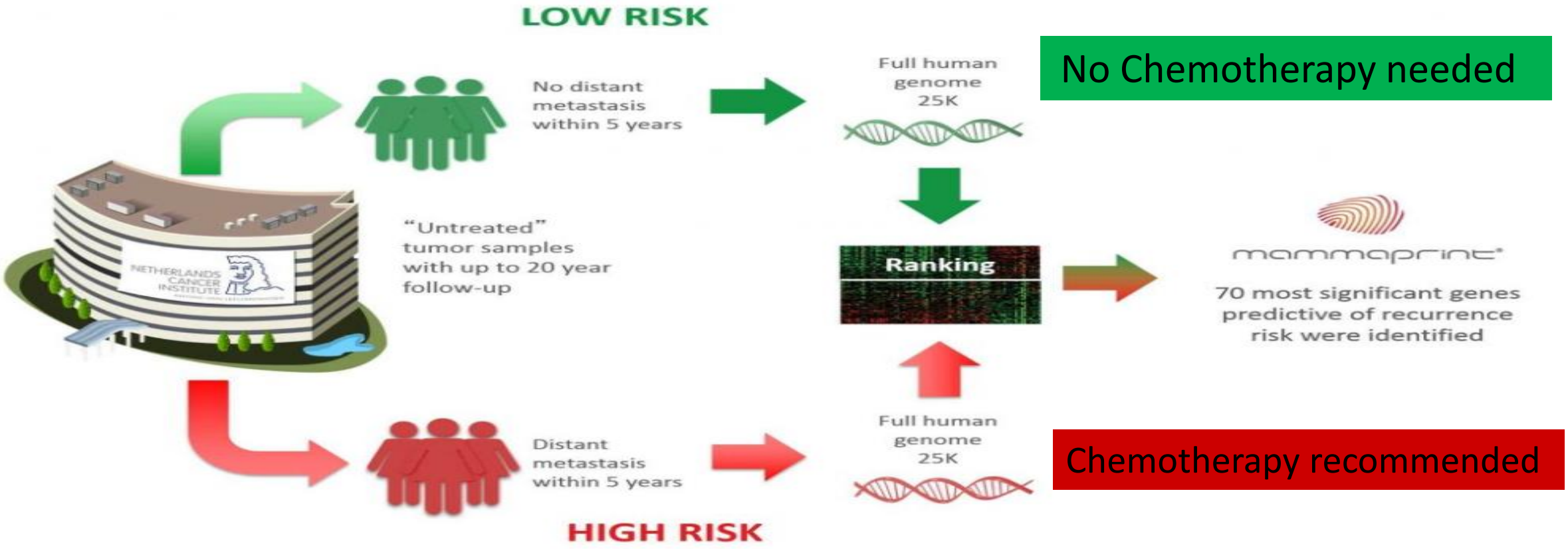

CDK4/6 inhibitor
pRb
E2F
Cyclin-D
Nucleus
Cell Cycle
STOP!
G1-S Checkpoint
S
DNA synthesis
G1
Growth
Rapid growth
G2
Mitosis
M


TECENTRIQ
PD-L1
Active T cell
Immune cell
PD-L1
TECENTRIQ
Tumor


DNA Repair Proteins
PARP Inhibitor
PARP


Chemotherapy e.g. taxane
HER3
HER4
HER2
Trastuzumab
HER activation
EGFR/HER1
Phenotype activation
VEGF
Cell-mediated Immunity
FcγRIII

Most patients do NOT need chemo



Breast Cancer 5 year survival

- Stage 0 or stage I: 100%
- Stage II: 93%
- Stage III: 72%
- Stage IV: 22%

Earlier detection = better survival

Earlier detection = smaller tumors = less treatment needed

American Cancer Society 2017

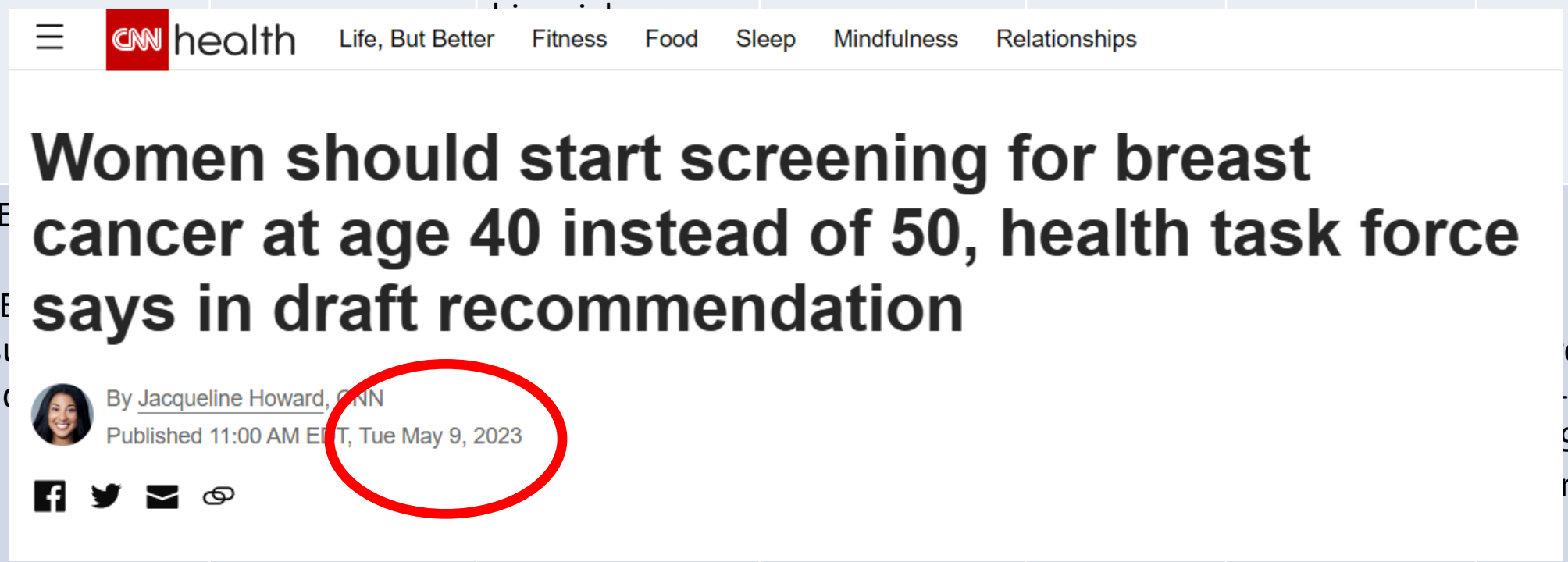
Risk factors patients can’t control

- Being female
- Getting older
- Family history of breast cancer
- Personal history of breast cancer
- Race
- Exposure to estrogen

Risk factors patients CAN control

- Weight
- Diet
- Exercise
- Alcohol
- Smoking
- Exposure to exogenous estrogen
- Pregnancy and breastfeeding
- Stress and Anxiety

	USPSTF	ACP	ACS	ASBrS	ACR	NCCN	ACOG
Start	50	50	45	40	40	40	40
Rate	Biennial	Biennial	Annual 45-55 then	Annual	Annual	Annual	Annual
Self or Clinical Breast Exam	BSE CBE Insu evi						May be ed -3 yrs age 9 nual age
Stop	75	LE ≥ 10 yrs	LE ≥ 10 yrs	LE ≥ 10 yrs	LE ≥ 5-7 yrs	Indiv.	Indiv.



CNN health Life, But Better Fitness Food Sleep Mindfulness Relationships

Women should start screening for breast cancer at age 40 instead of 50, health task force says in draft recommendation

By Jacqueline Howard, CNN

Published 11:00 AM EDT, Tue May 9, 2023

40 vs 50

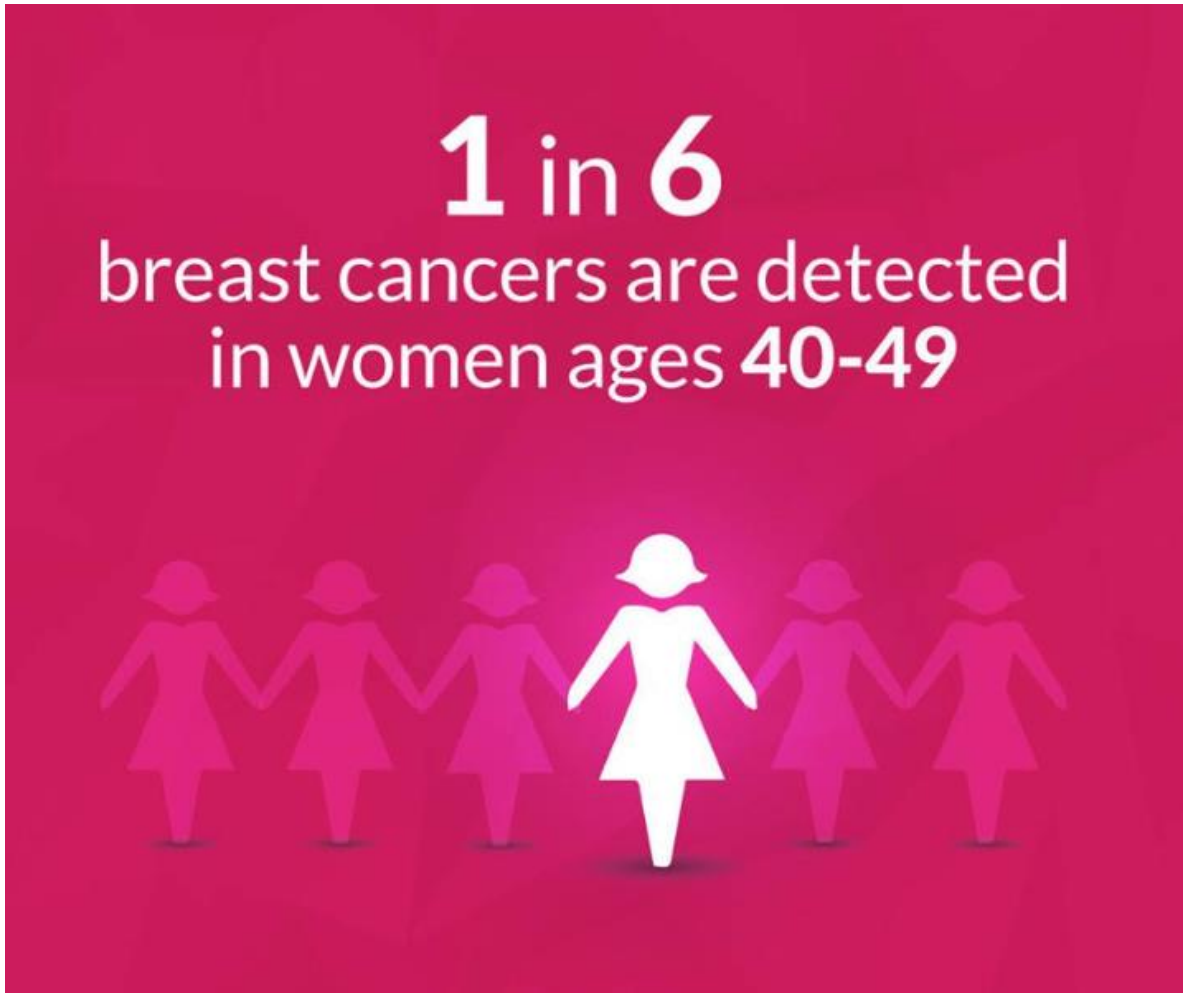


Table 1. Estimated New Female Breast Cancer Cases and Deaths by Age, US, 2017

	In Situ Cases		Invasive Cases		Deaths	
Age	**Number**	**%**	**Number**	**%**	**Number**	**%**
<40	1,610	3%	11,160	4%	990	2%
40-49	12,440	20%	36,920	15%	3,480	9%
50-59	17,680	28%	58,620	23%	7,590	19%
60-69	17,550	28%	68,070	27%	9,420	23%
70-79	10,370	16%	47,860	19%	8,220	20%
80+	3,760	6%	30,080	12%	10,910	27%
All ages	**63,410**		**252,710**		**40,610**	

Estimates are rounded to the nearest 10. Percentages may not sum to 100 due to rounding.

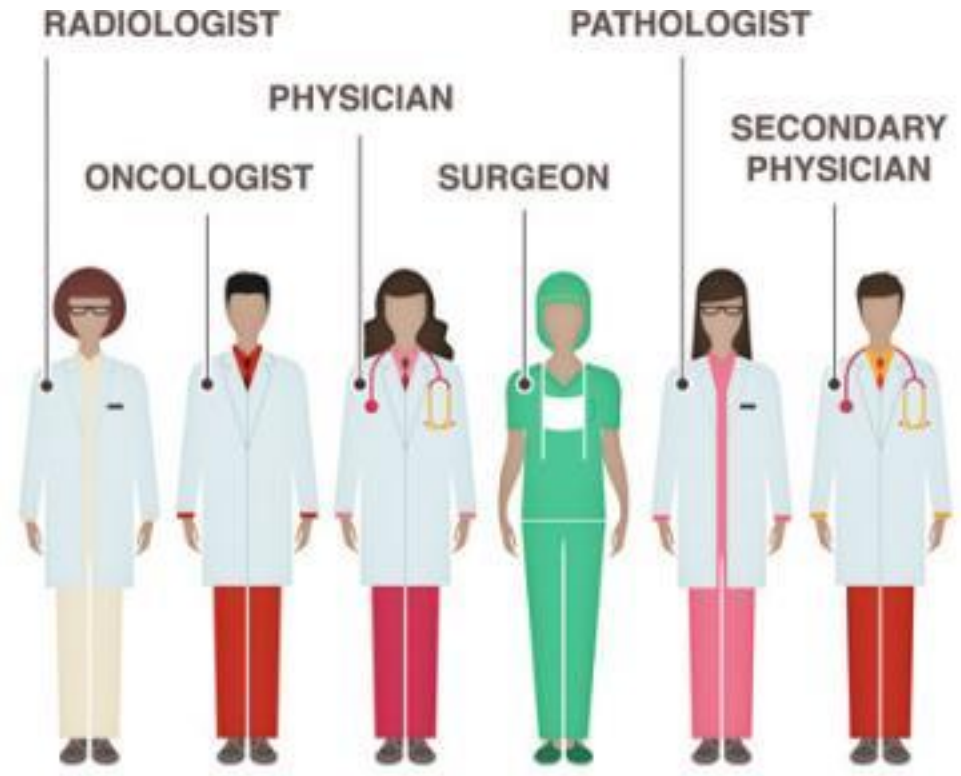
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf

40 vs. 50

- Although number of lives saved is smaller compared to age 50 and above, ~40% of years of life saved by mammography are among women in their 40s.
- Typically more aggressive, less indolent cancers in this age range.
- More genetic mutations found in this age range.

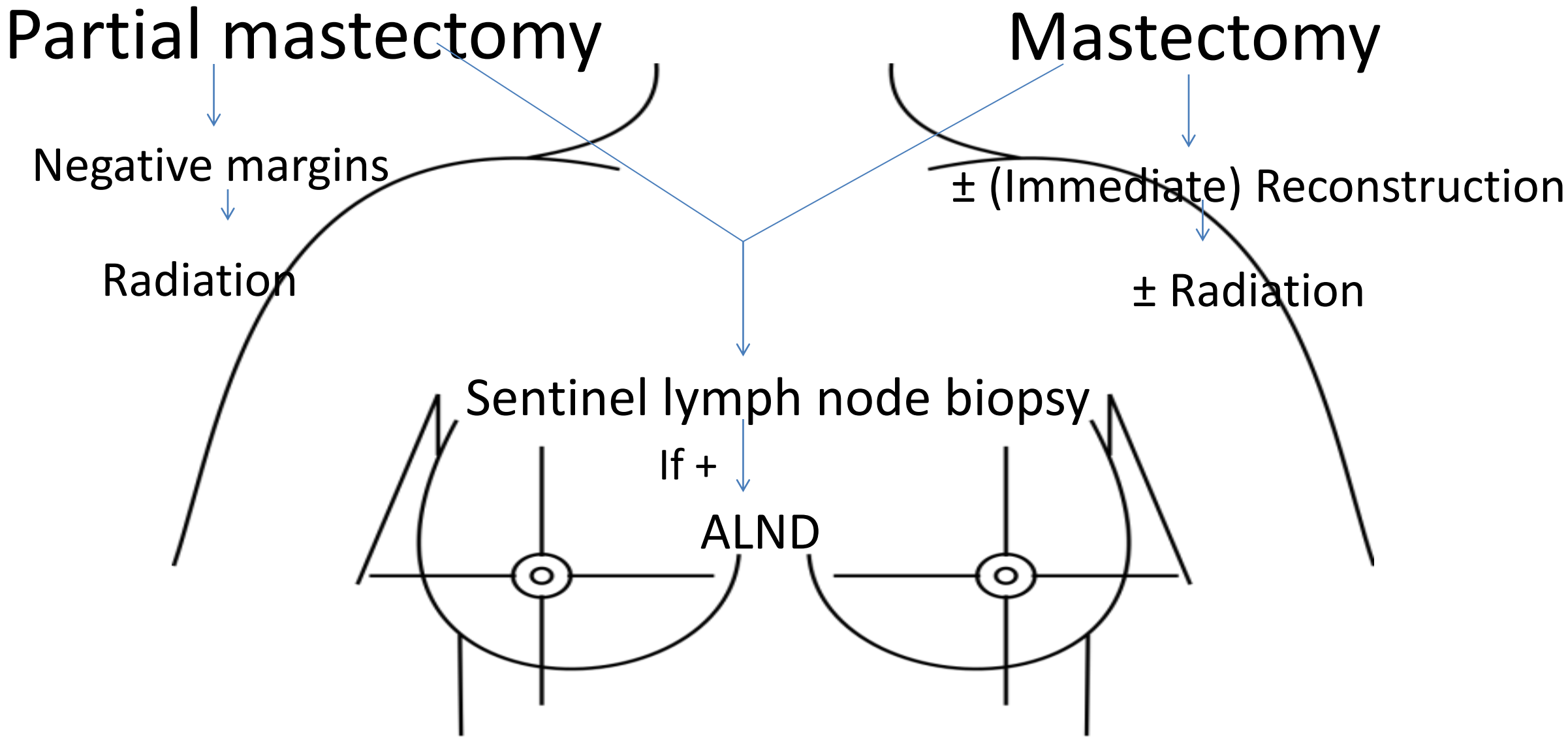
Multidisciplinary Team Approach

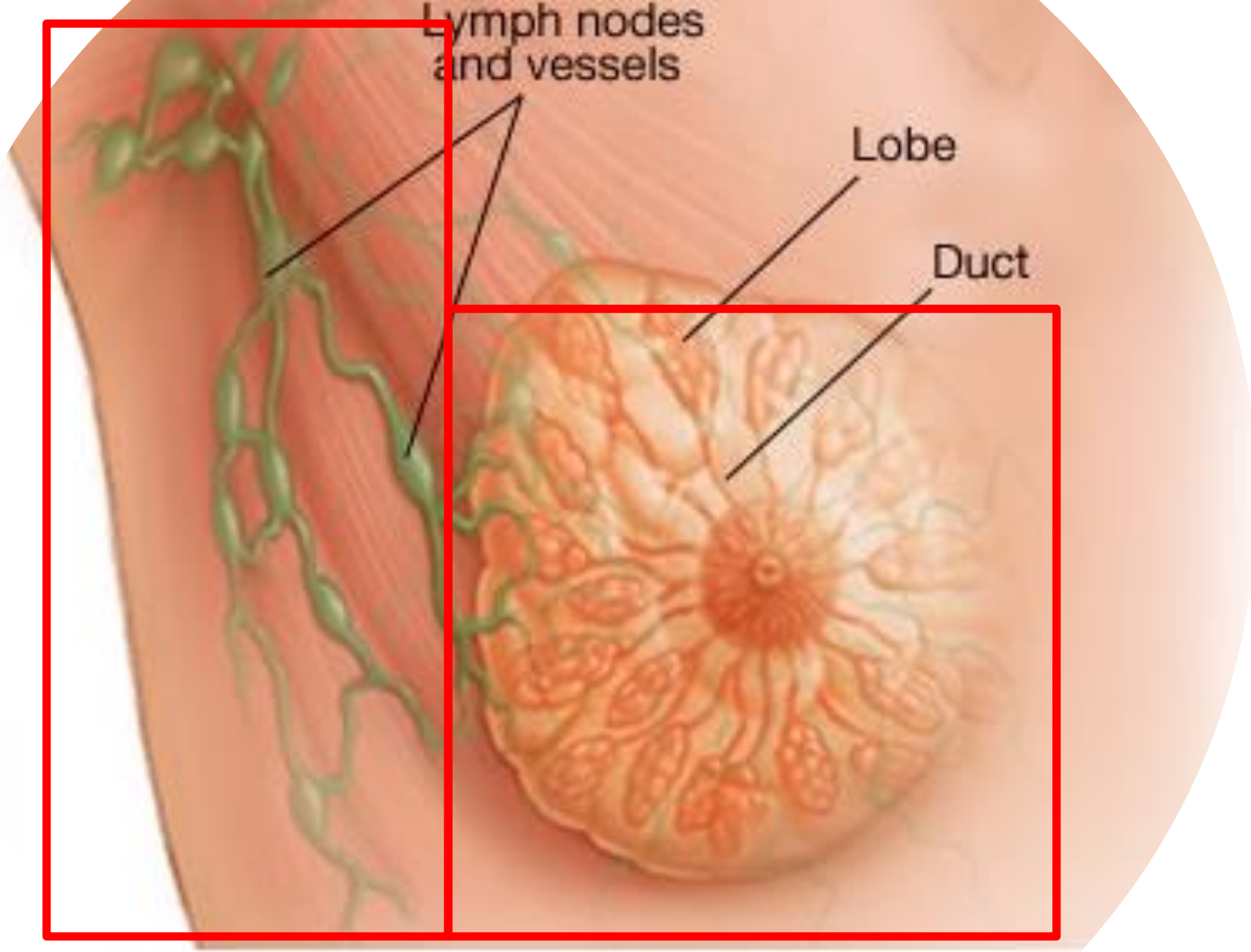
- **Breast Surgeon**
- Medical Oncology
- Radiation Oncology
- Plastic Surgeon
- Breast Imagers/Radiologist
- Pathologist
- Dedicated ARNP, RN, LPN, MAs
- Nurse Navigator
- Social Worker
- Multidisciplinary Tumor Board
- Complementary Medicine



- NSABP B04 (1971-1985) – allowed women to avoid radical (Halsted) mastectomy.
- Milan group (1970s) – adding chemotherapy regimen CMF reduces breast cancer recurrence.
- NSABP B06 (1976-1984) – allowed women to keep their breasts safely (lumpectomy) by adding radiation.
- NSABP B14/P-1/B24 – adding Tamoxifen reduces subsequent breast cancer by 50%.
- NSABP B32 (1999-2004) – avoided axillary dissection safely (reduce lymphedema).

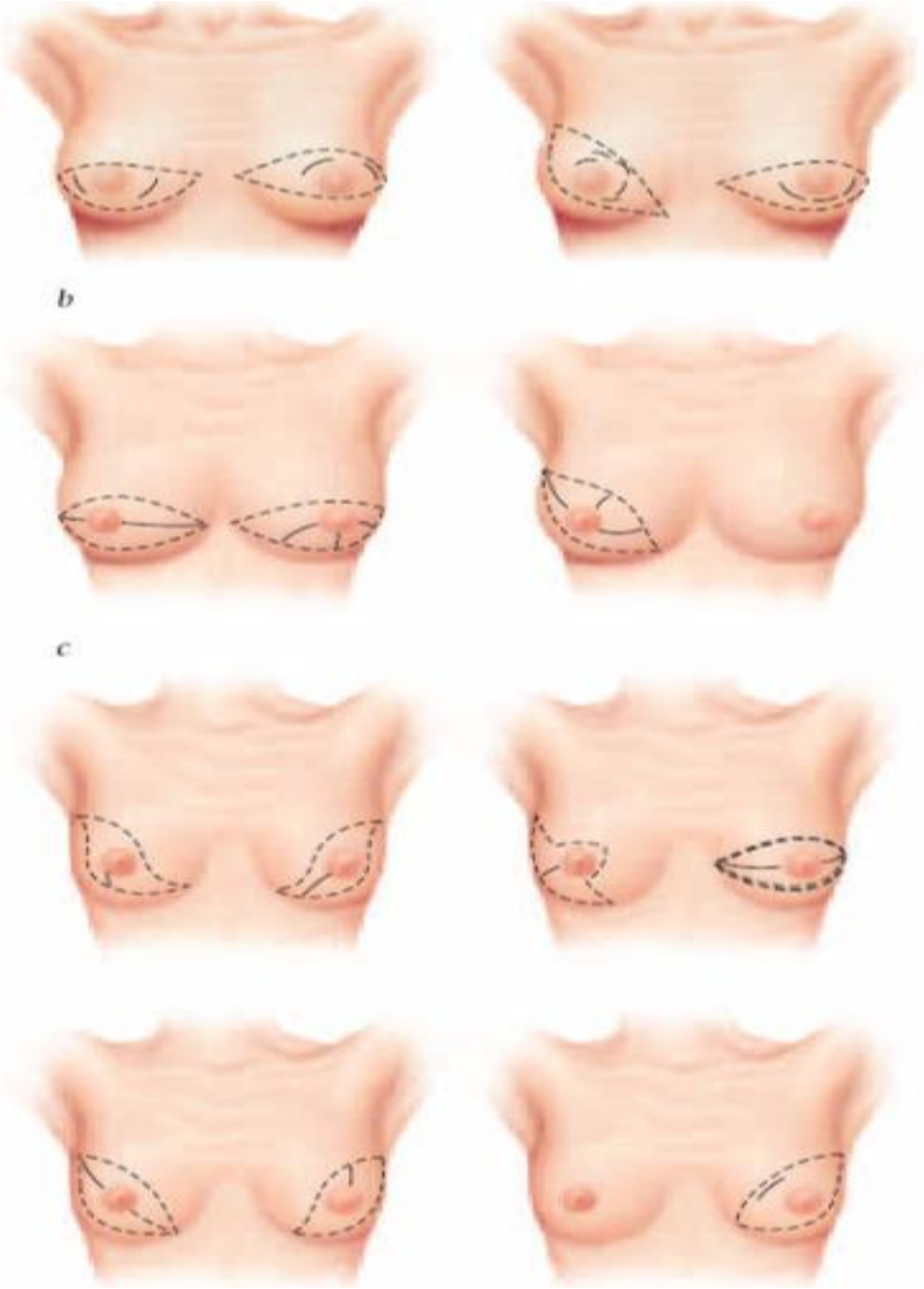
- ACOSOG Z11 (2004-2011) – avoided axillary dissection despite cancer spreading to the lymph nodes (reduce lymphedema).
- CALGB 9343 (1994-1999)/PRIME II (2015) – avoid radiation in older women who undergo lumpectomy.
- NSABP B31/HERA (2000-2005) – addition of Herceptin to HER-2 positive breast cancers reduced a second cancer/death by 50%.
- TAILOR Rx (2015)/MINDACT (2016) – using genomic data to reduced chemotherapy use by 70%. Era of personalized medicine has begun.
- RxPonder (2021) – using genomic data to safely avoid chemotherapy in ER+ breast cancer in women with 1-3 metastatic axillary lymph nodes.


Partial mastectomy
Mastectomy
Negative margins
Radiation
± (Immediate) Reconstruction
± Radiation
Sentinel lymph node biopsy
If +
ALND

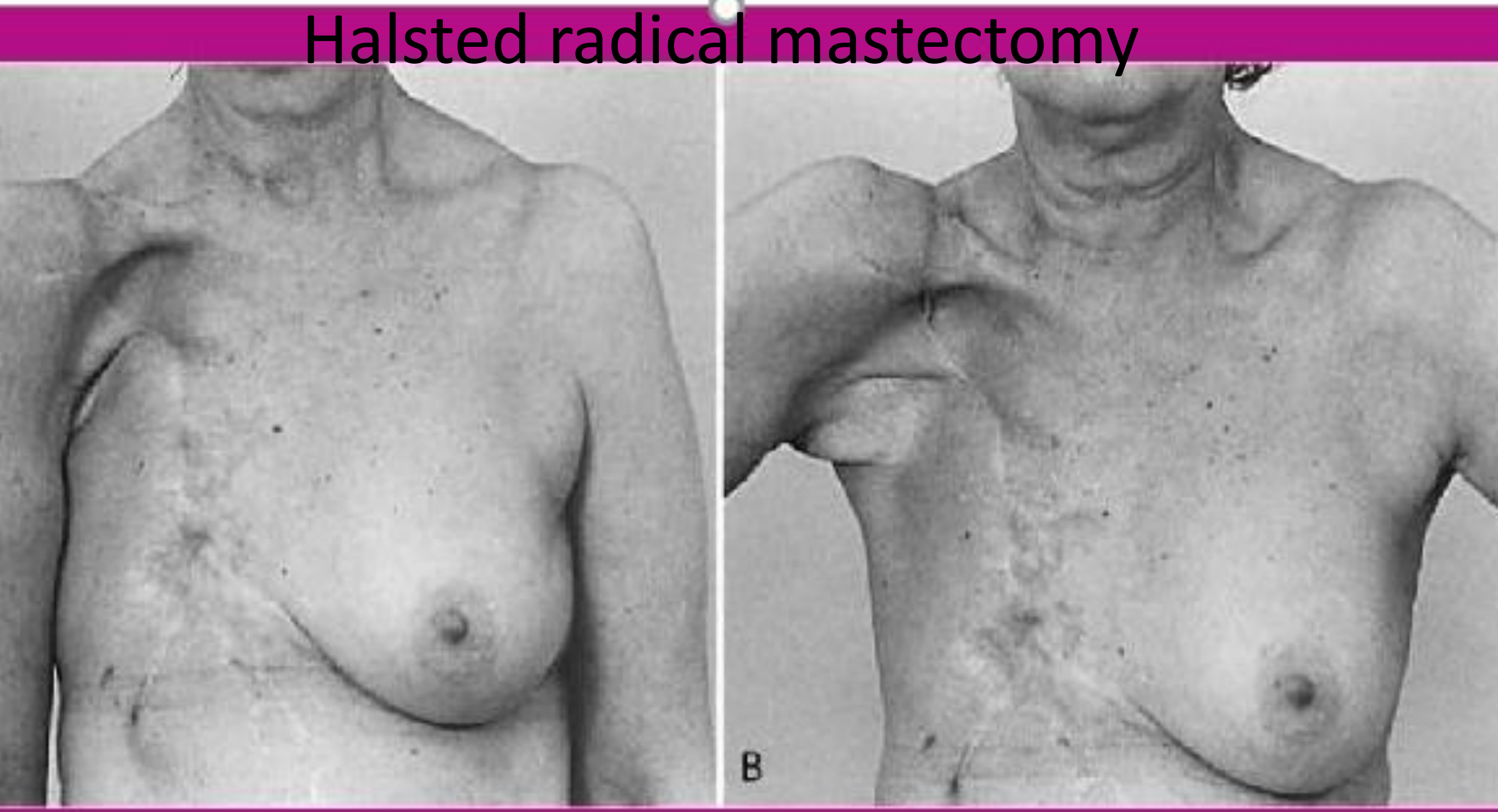


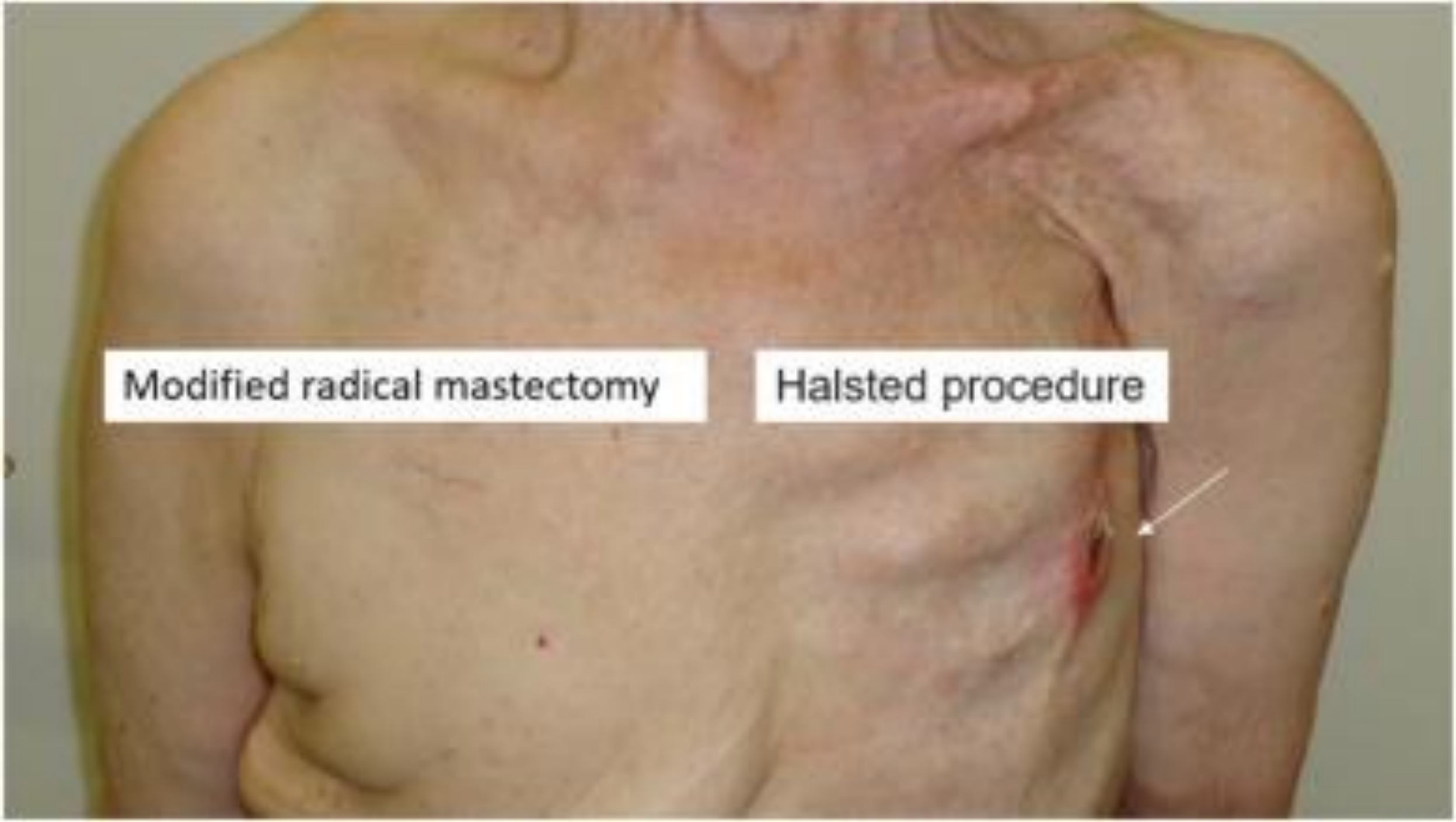
Mastectomies

- Indications:
  - Multi-centric
  - Large tumor/small breast
  - Diffuse malignant appearing calcifications
  - Hx of radiation
  - Pregnancy
  - Persistently positive margins
  - Patient choice
  - Prophylaxis

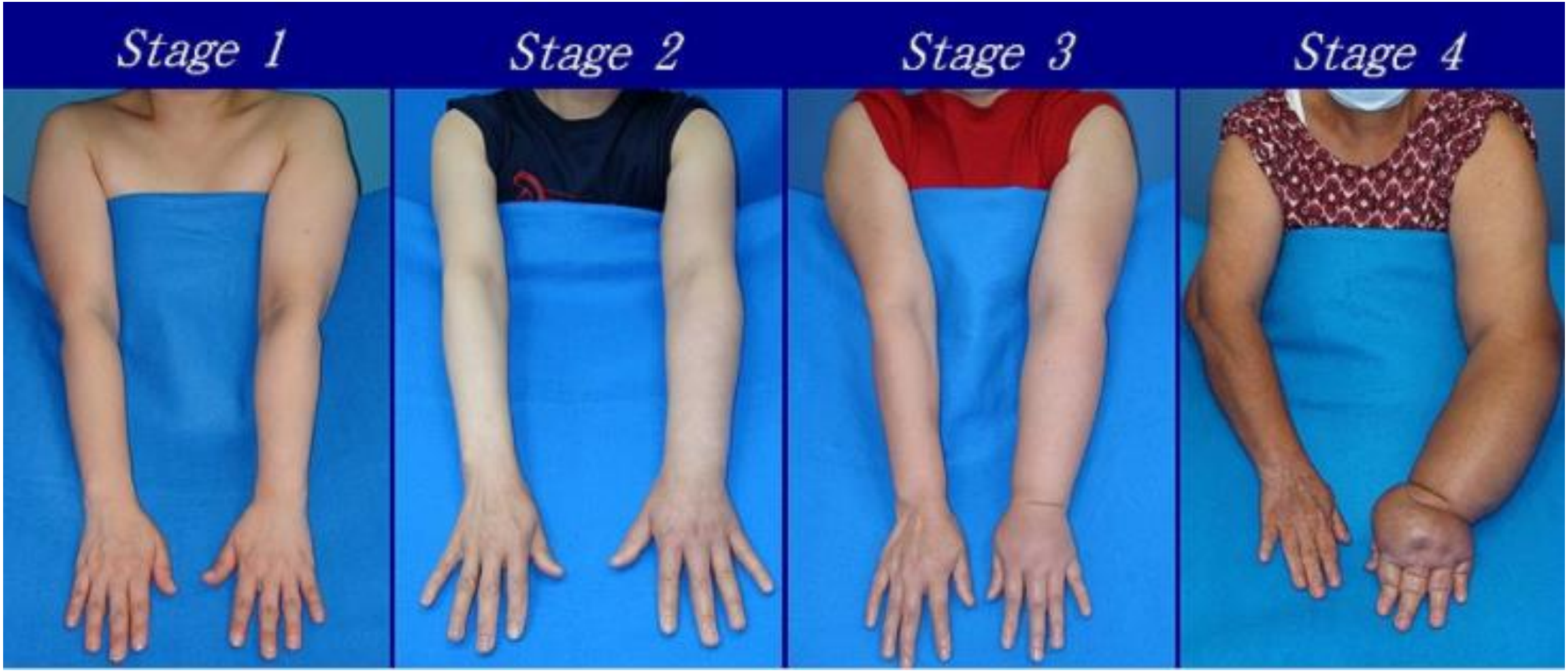


Halsted radical mastectomy

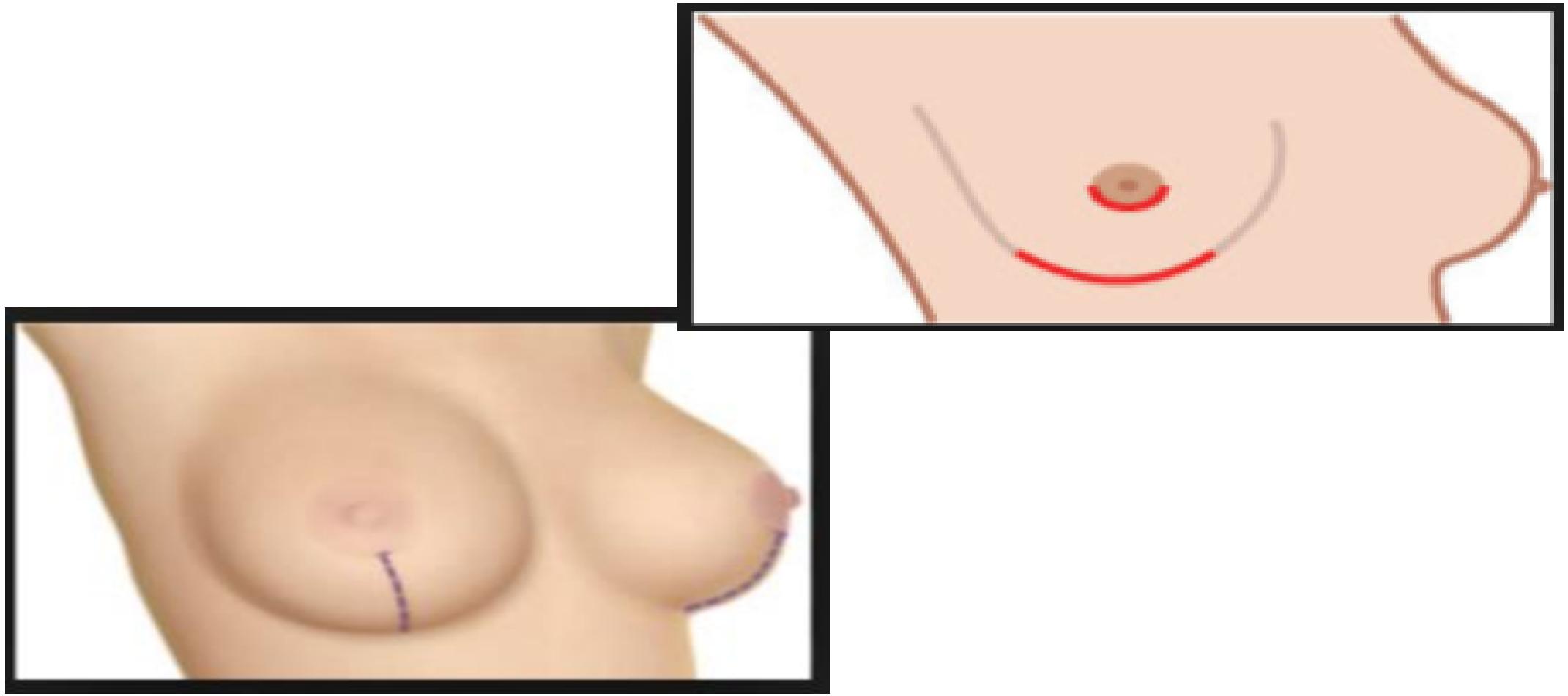



Modified radical mastectomy
Halsted procedure

Lymphedema

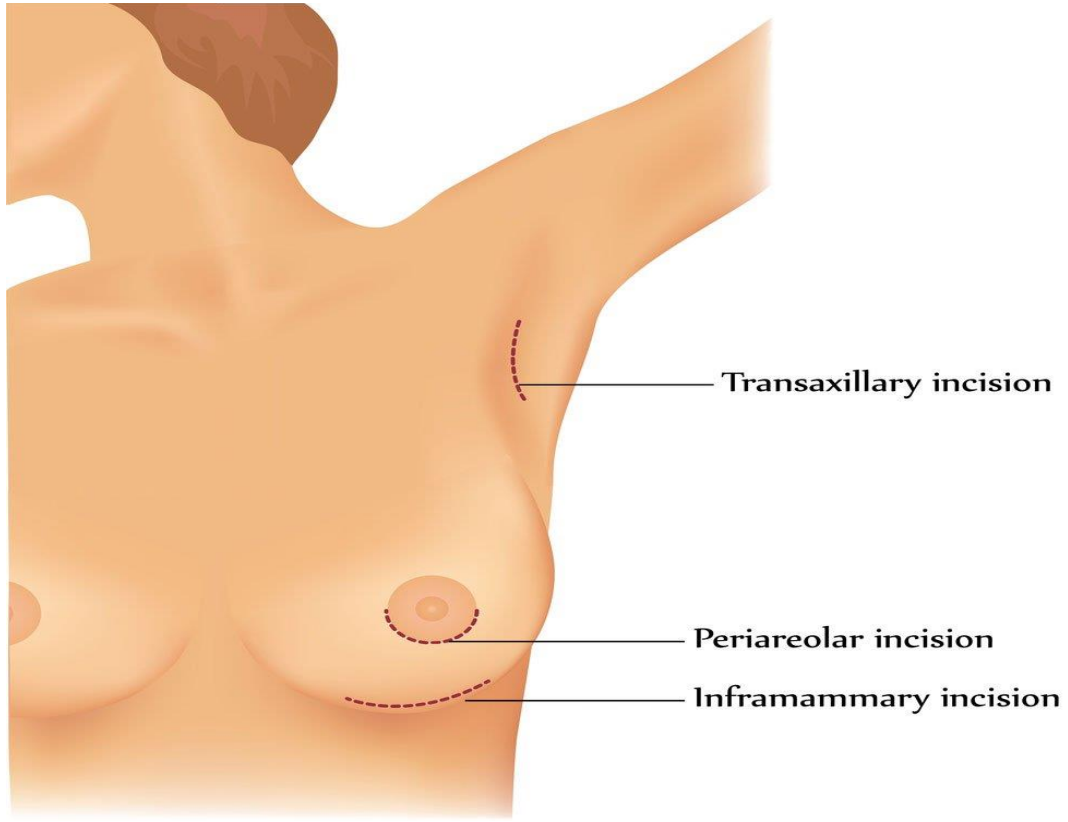


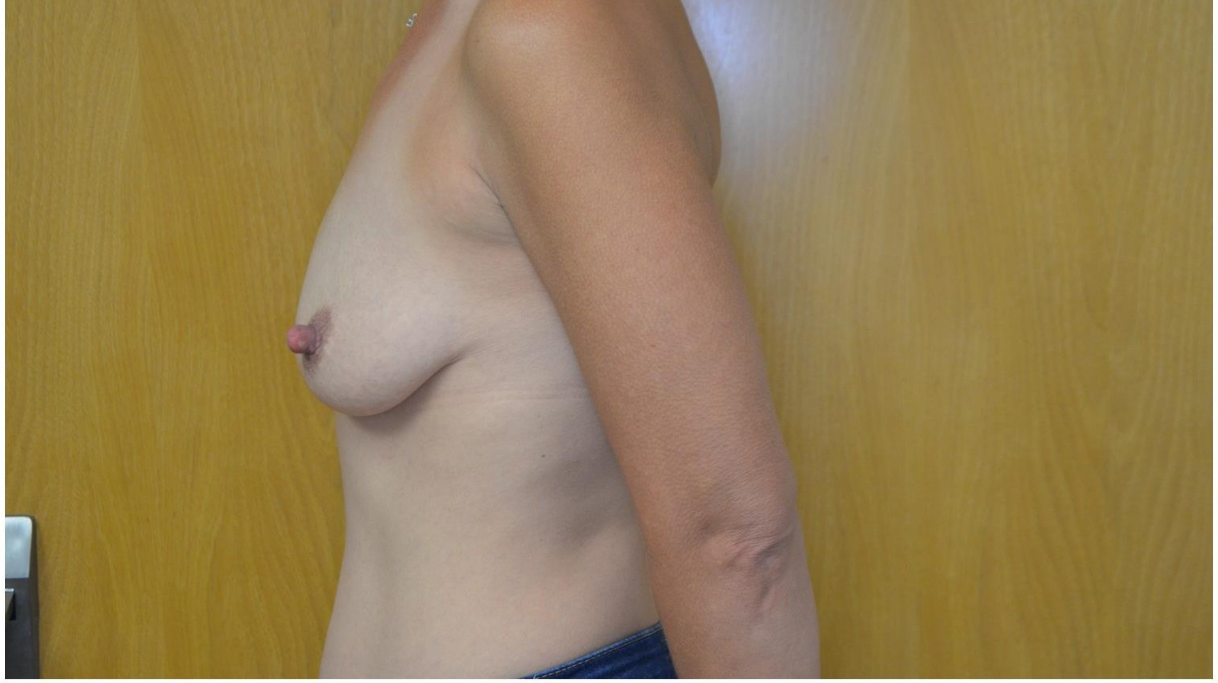
Nipple sparing

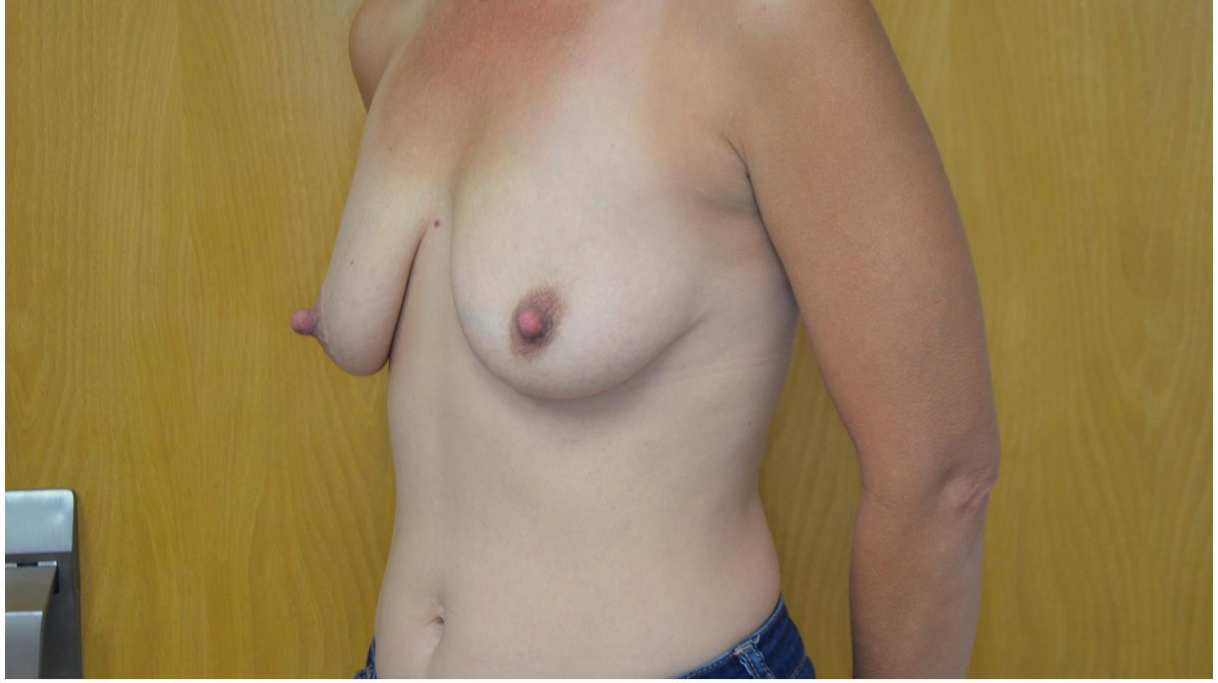


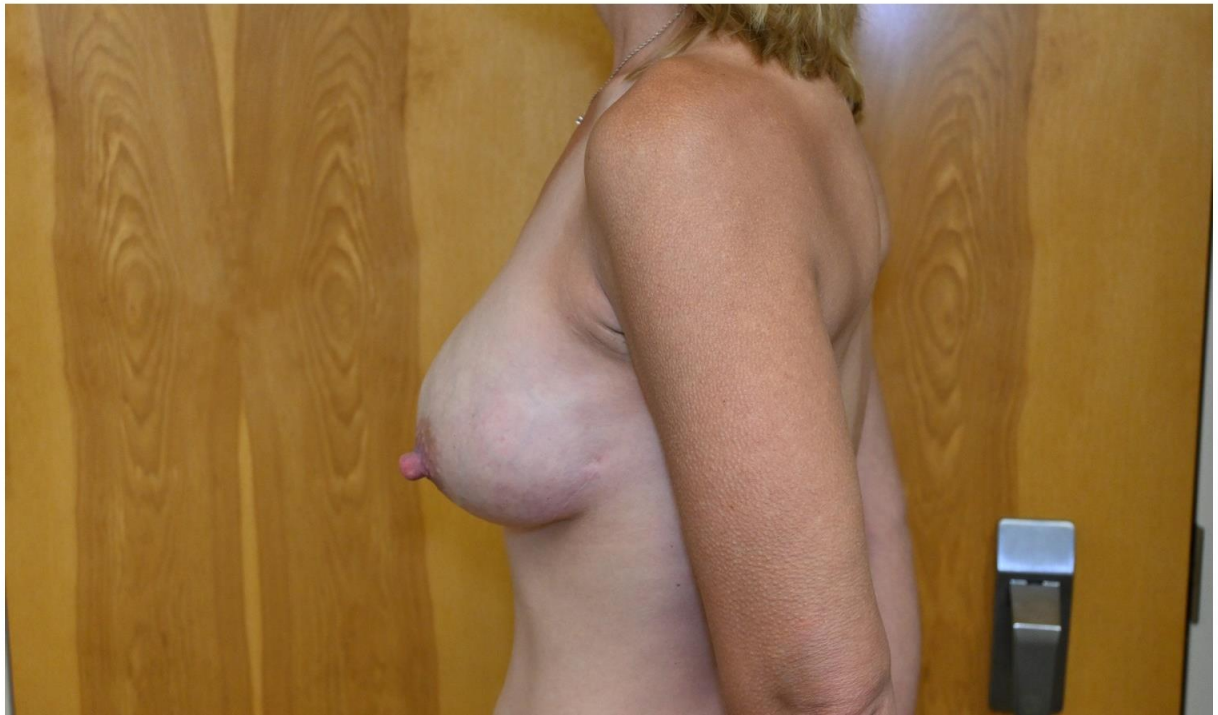
What is Oncoplastic Surgery?

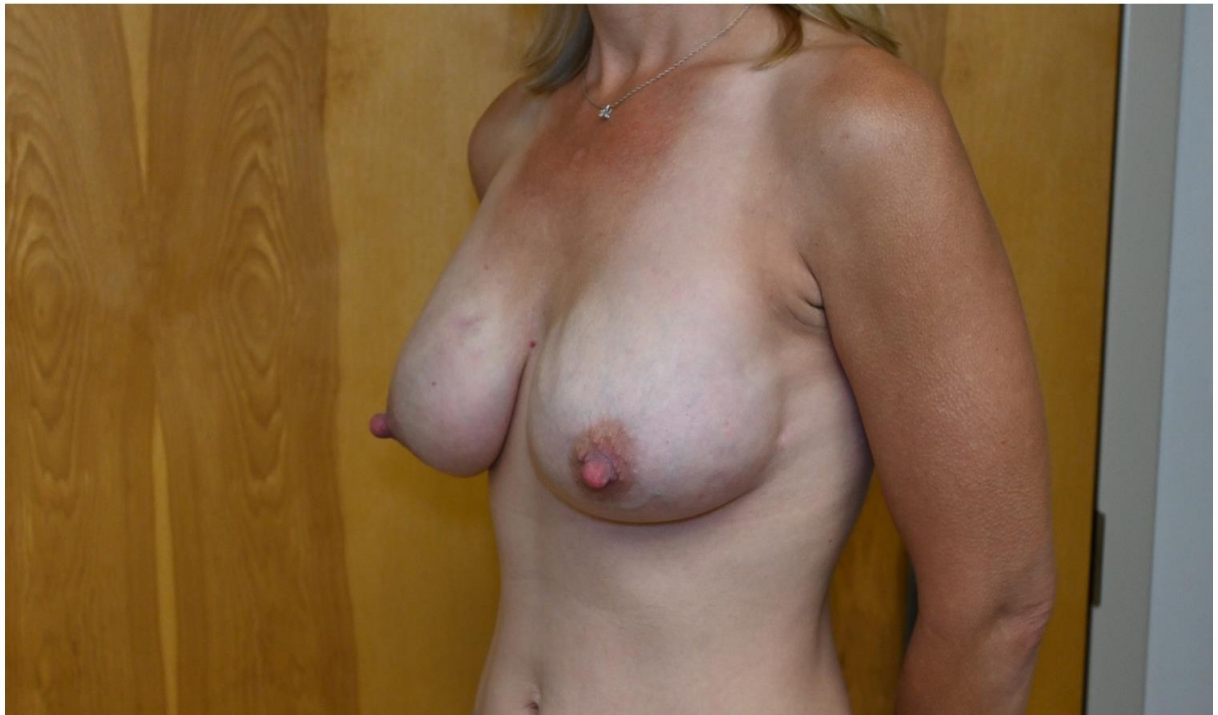
- Incisions limited to:
  - IMF, peri-areolar, axillary
- Balancing procedure on the opposite breast, with Plastic Surgeon
- Lumpectomies:
  - Tissue rearrangement
- Mastectomies:
  - Nipple- or skin-sparing
- Oncologically safe

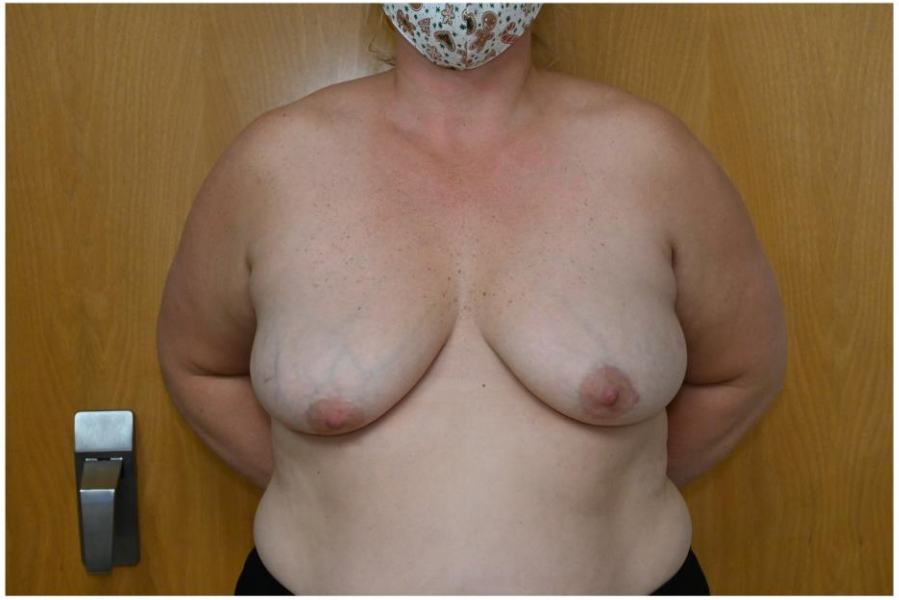


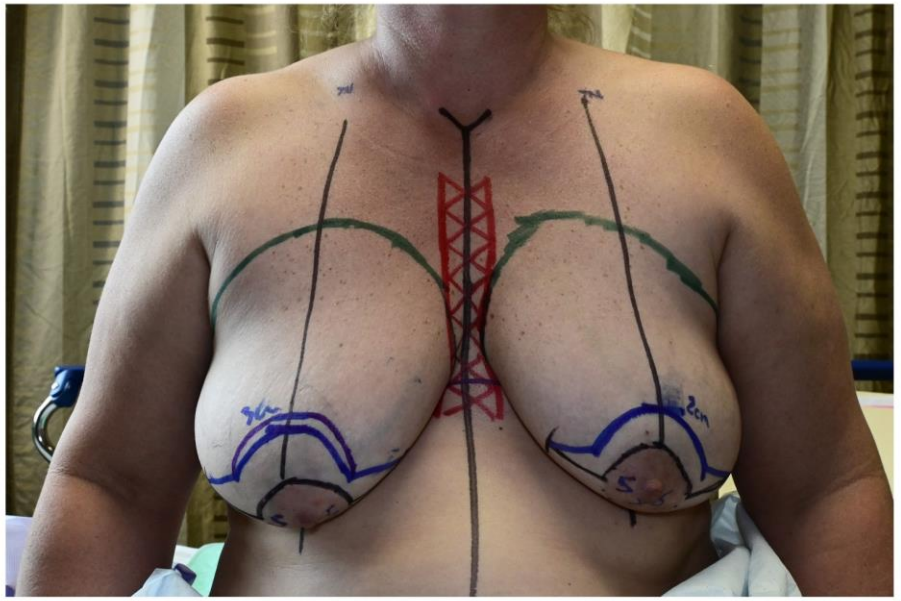


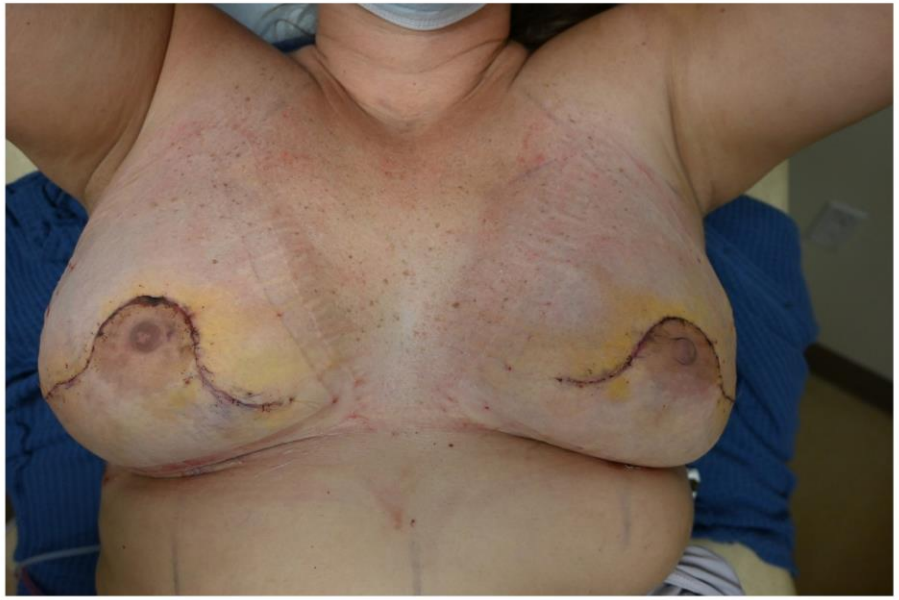


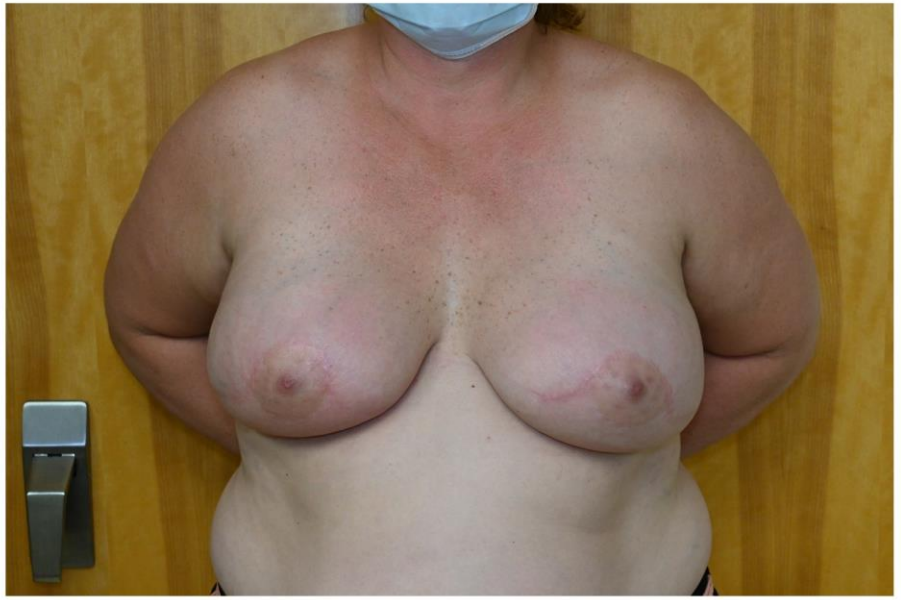




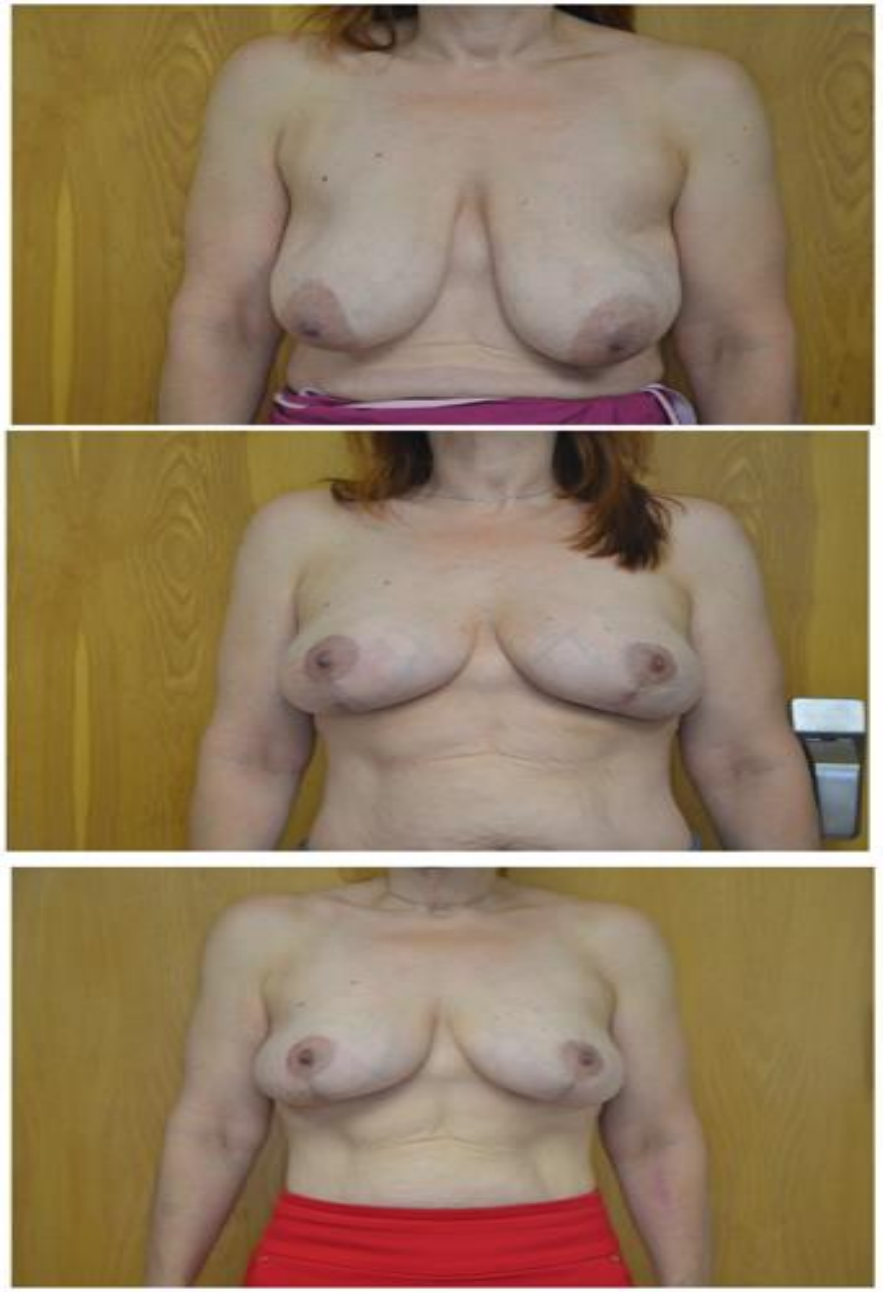




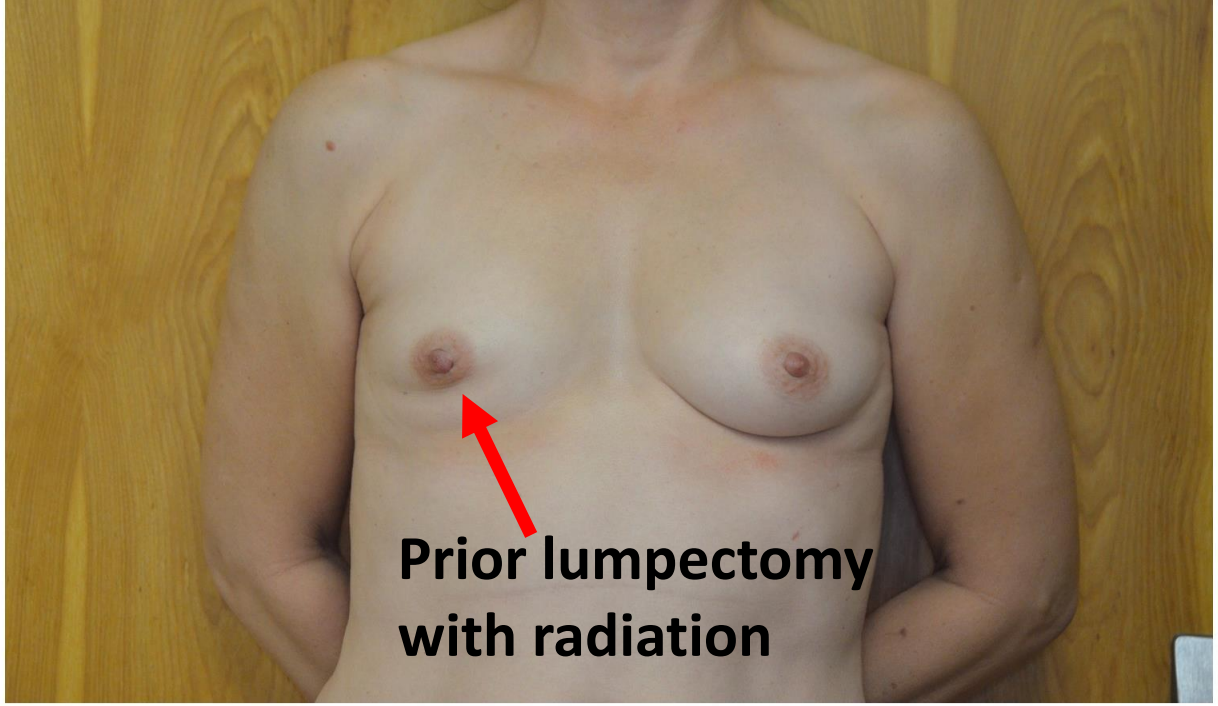


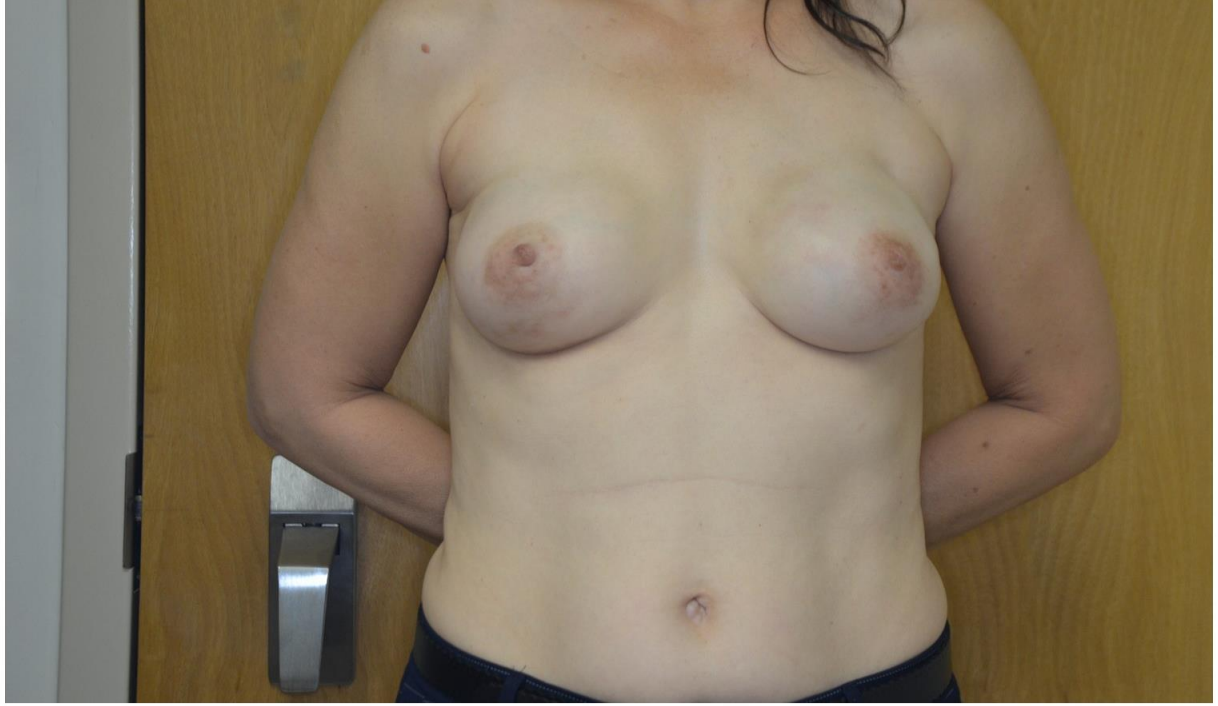


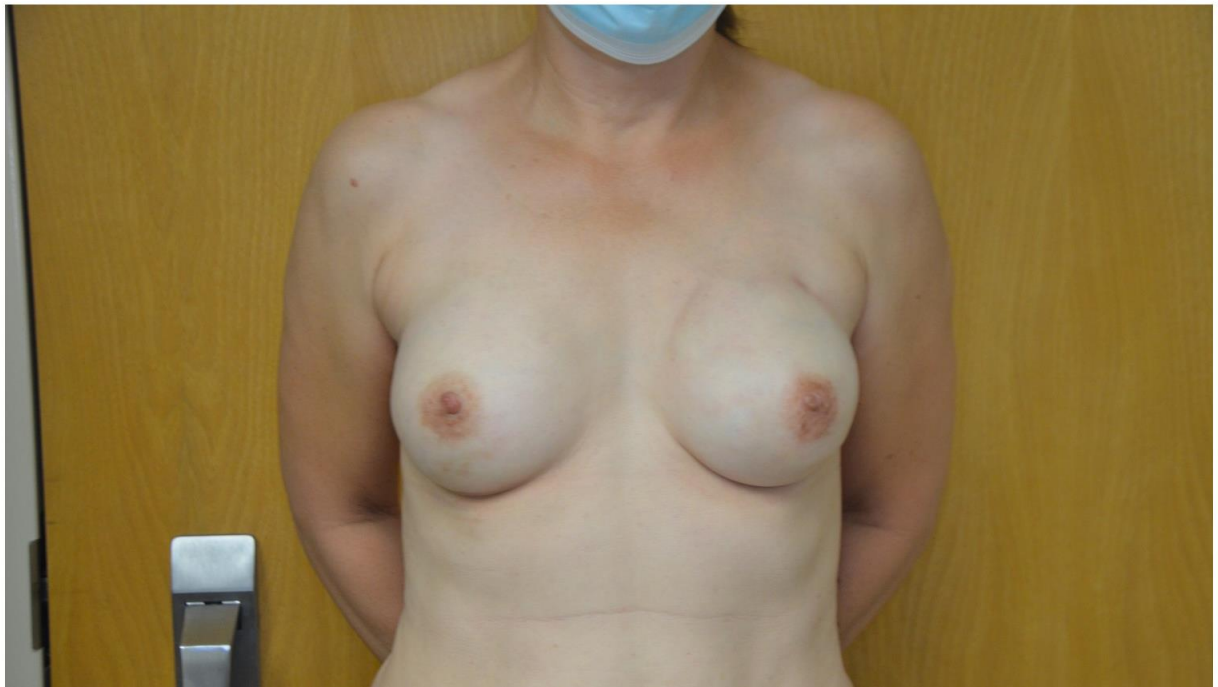
Single-staged nipple-sparing mastectomy with silicone implants

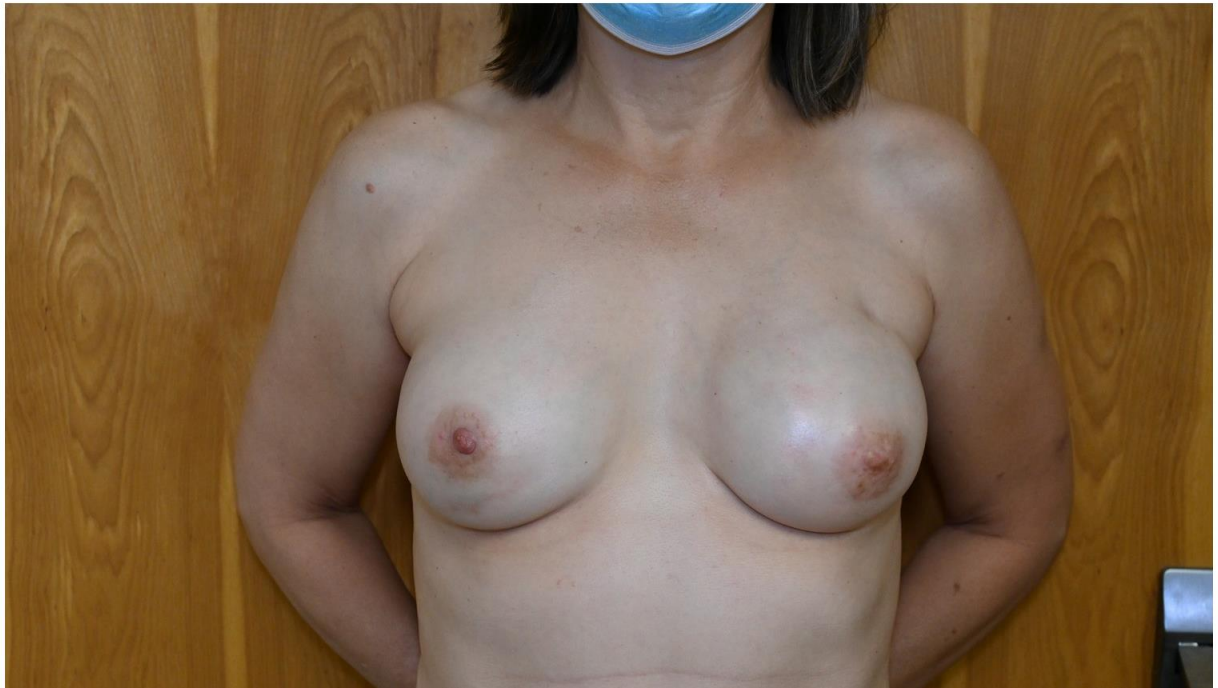


Two-staged reduction mammaplasty to nipple-sparing mastectomy with implants

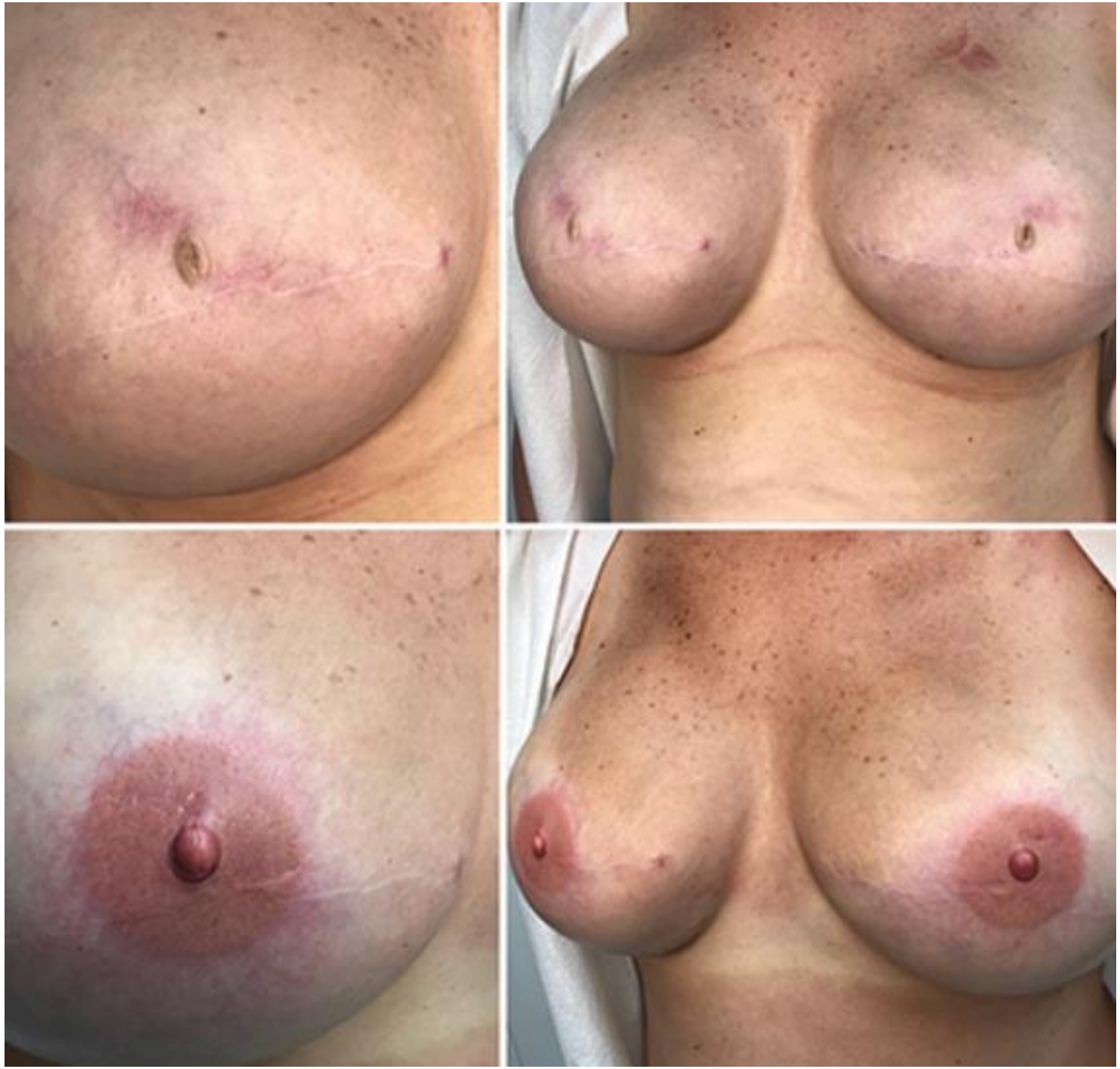

Prior lumpectomy
with radiation



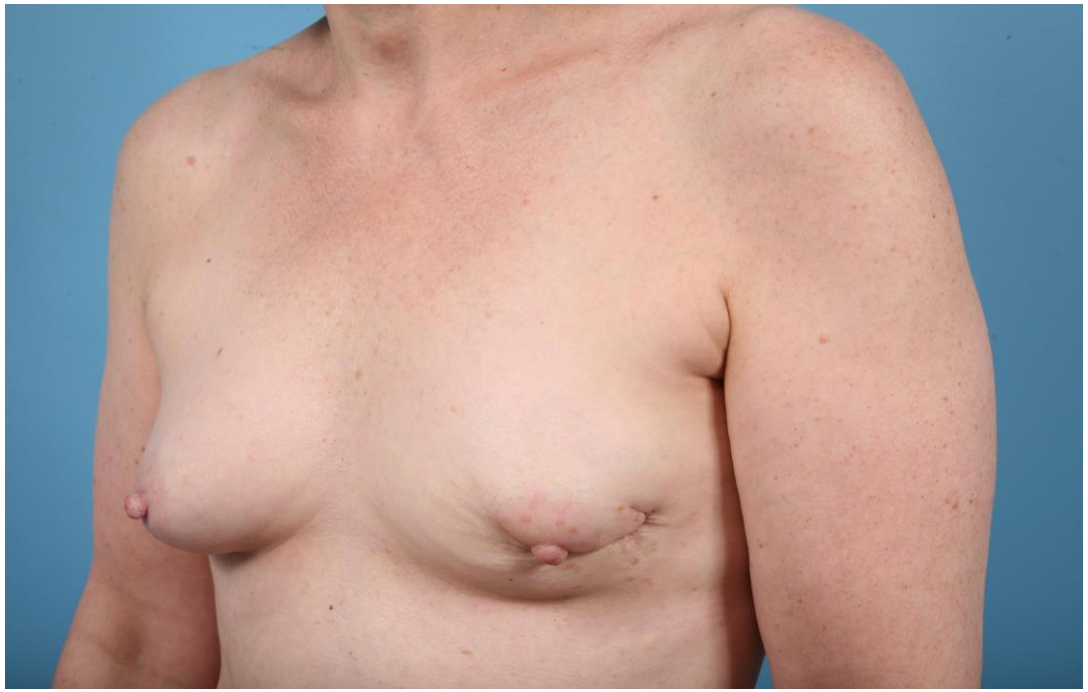


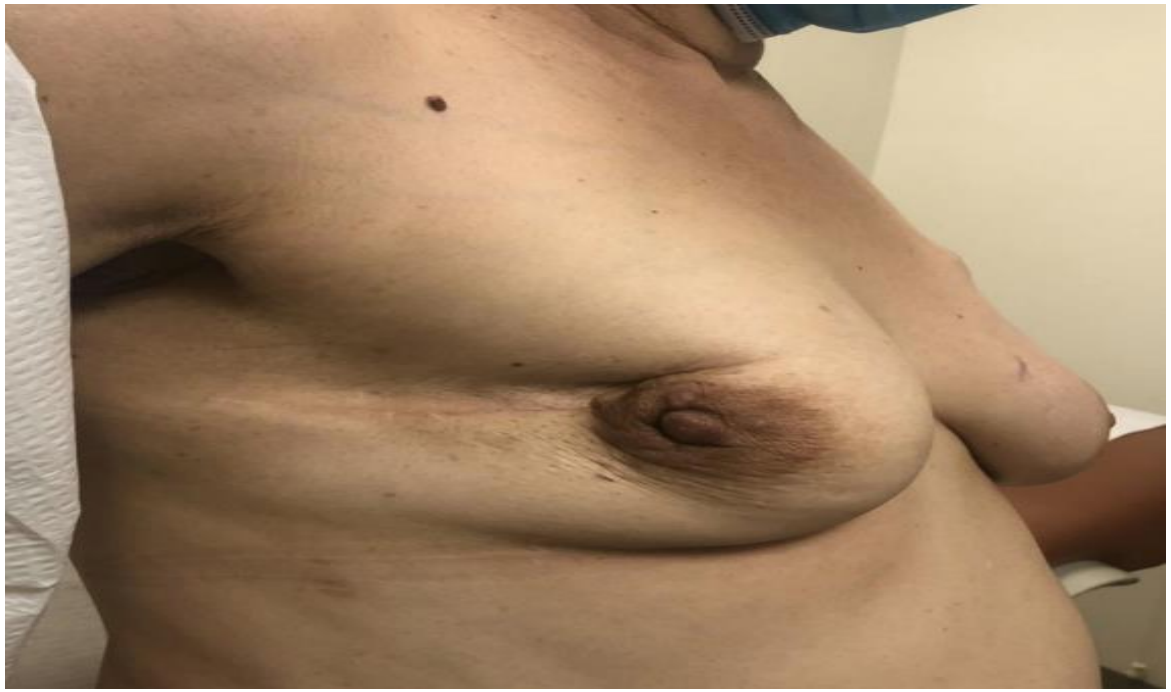


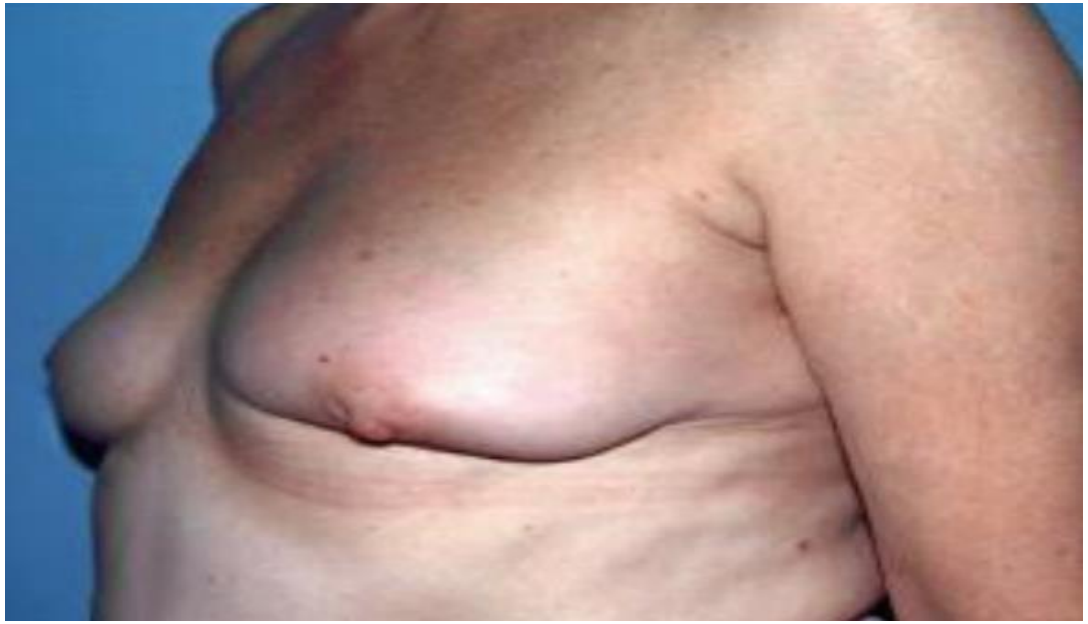
Oncoplastic reduction with radiation

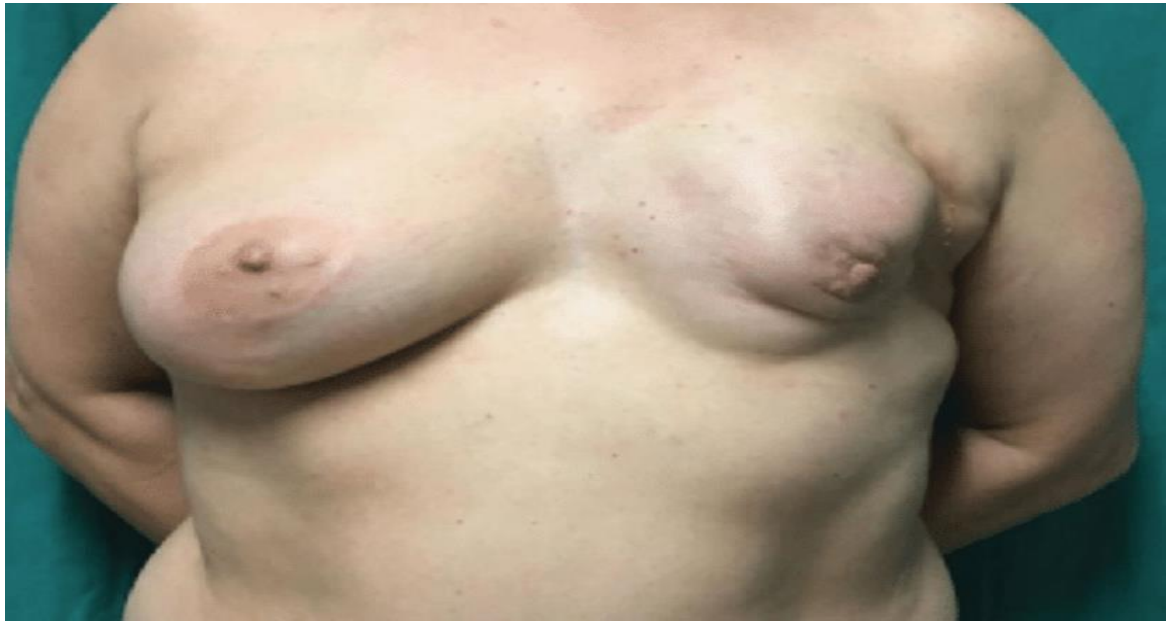


Skin-sparing mastectomy with implants and 3-D nipple tattooing

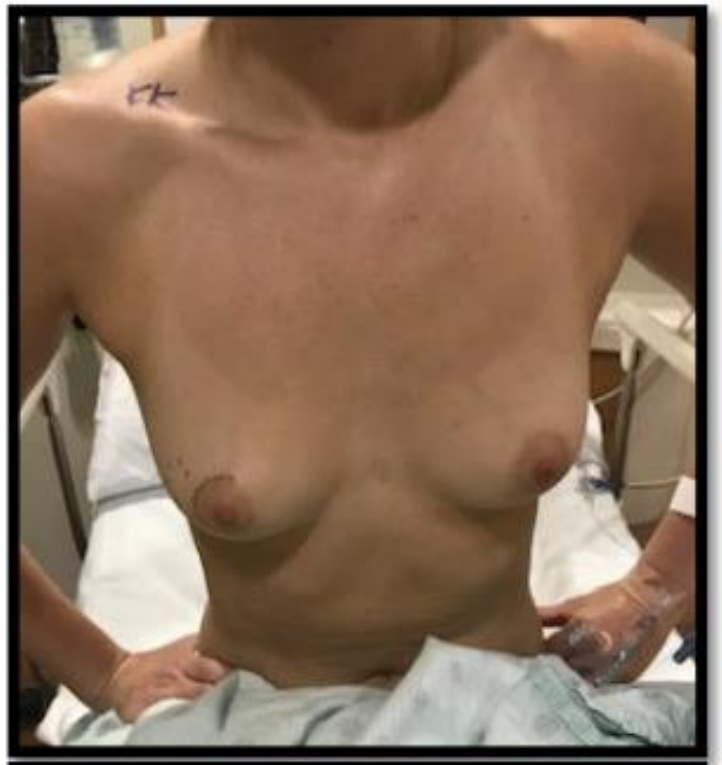


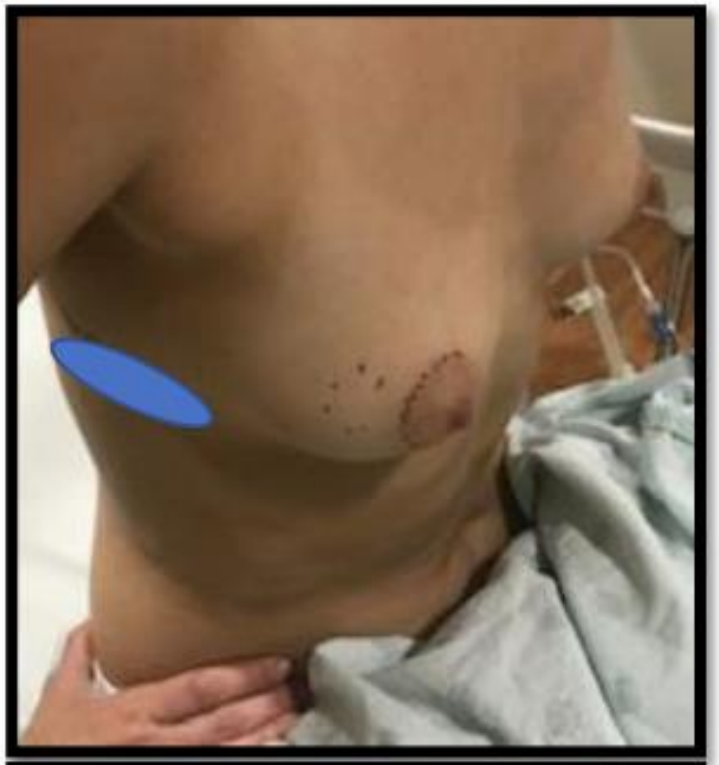






Pre-op

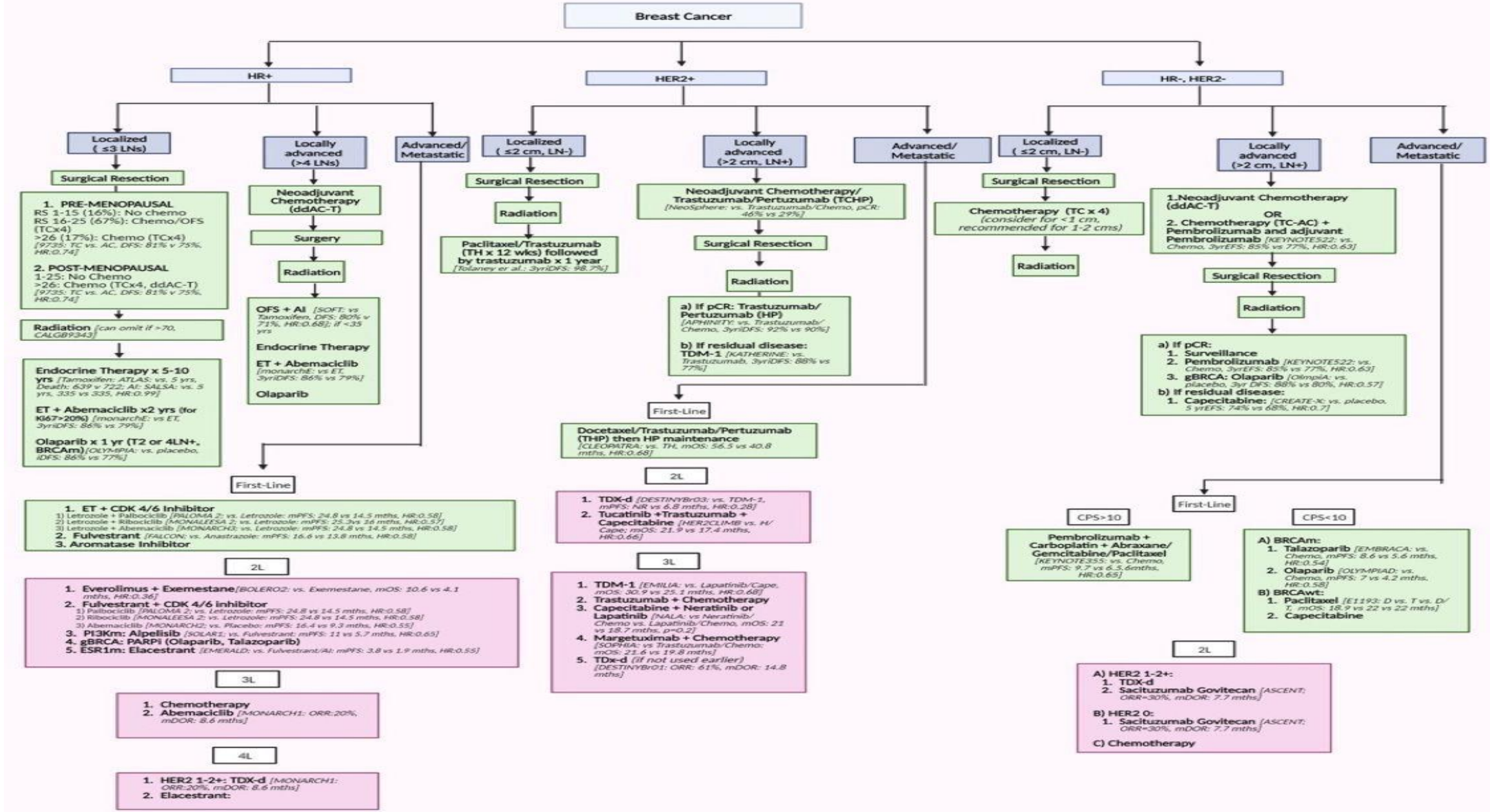




6 month Post-op

Are all breast cancers treated similarly?

NO!



Created by: Aakash Desai, @ADesaiMD. Disclaimer: This is meant to be used as a study guide for medical oncology fellows. This does not represent medical advice. May not always include updated information on all clinical trials or represent all treatment options.

The biology of breast cancer: receptors

Hormone Receptors:

- Estrogen Receptor
  - Negative <1%
  - Weakly positive 1-10%
  - Positive >10%
- Progesterone Receptor
- HER2/neu Receptor
  - If equivocal, sent for FISH analysis
- Ki67
  - Proliferation marker (<10%,10-20%, or >20%)

Grade:

Degree of differentiation, how much it looks like normal tissue

Grade 1: low, well differentiated

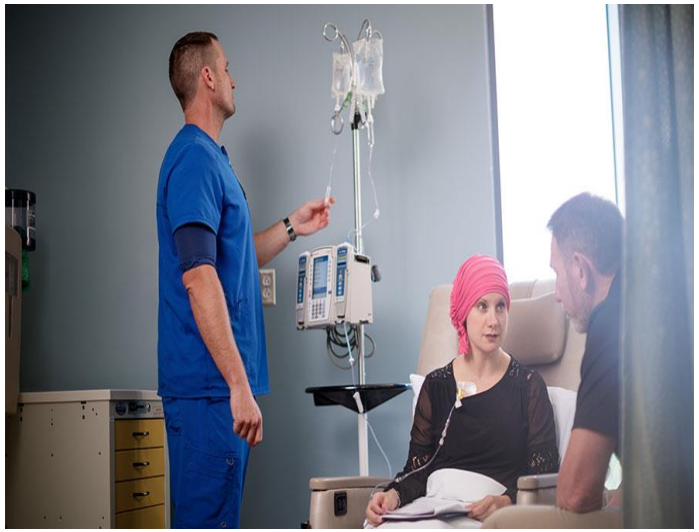
Grade 2: intermediate, moderately differentiated

Grade 3: high, poorly differentiated

Who gets Neoadjuvant therapy?

- Patient who want lumpectomy but have large tumors
- HER2+ tumors >2cm *OR* positive nodes
- Triple negative tumors (>2cm and/or positive nodes)
- ER+ tumors >2cm *OR* positive nodes – use genomic data
  -especially premenopausal women
- Locally Advanced Disease (T4, N2)
- Patients enrolled in clinical trials

Adjuvant Systemic Therapy



- Chemotherapy:
  - Triple negative breast cancer
  - HER-2 positive breast cancer
  - Estrogen positive breast cancer with genomic testing (Oncotype DX or Mammaprint)

- Hormonal/Endocrine Therapy:
  - Indications: ER/PR+ cancers (DCIS and invasive), high risk lesions
  - Duration: 5-10yrs (Tamoxifen, Aromatase inhibitors, Raloxifene)

Adjuvant Systemic Therapy - CDK 4/6 inhibitors

Table 1. Summary of FDA-Approved CDK Inhibitors

Agent	Dosing	Drug Interaction	Notable Toxicities
Palbociclib (Ibrance)	125 mg po once daily for 21 days in a 28-day cycle with food	CYP3A4 substrate	Neutropenia, leukopenia, fatigue, nausea, infection, headache, ILD
Ribociclib (Kisqali)	600 mg po daily for 21 days in a 28-day cycle with or without food	CYP3A4 substrate	Neutropenia, leukopenia, fatigue, nausea, infection, headache, ILD, arthralgia, QTc prolongation, hepatotoxicity
Abemaciclib (Verzenio)	150 mg or 200 mg po bid with or without food	CYP3A4, Pgp, BCRP substrate	Neutropenia, fatigue, nausea, vomiting, headache, diarrhea, dysgeusia, ILD

BCRP: breast cancer resistance protein; CDK: cyclin-dependent kinase; ILD: interstitial lung disease; Pgp: P-glycoprotein. Source: References 6, 8.

Table 2. Summary of Phase III Clinical Trials of CDK4/6 Inhibitors

Study and Population	Treatment Arms	Median Follow-Up Duration	PFS (95% CI)	OS	ORR[a]
PALOMA-2: First-line for postmenopausal women (N = 666)	Palbociclib + letrozole vs. placebo + letrozole	**Initial Report**			
		23 mo	24.8 mo (2.1-NR) vs. 14.5 mo (12.9-17.1); HzR, 0.58 (0.46-0.72); *P* <.001	—	42.1% (37.5-46.9) vs. 34.7% (28.4-41.3); *P* = .06
		Extended Follow-up			
		38 mo	27.6 mo (22.4-30.3) vs. 14.5 mo (12.3-17.1); HzR, 0.563 (0.461-0.687); *P* <.0001	—	—
PALOMA-3: Second-line for pre-, peri-, or postmenopausal women who relapsed or progressed on ET (N = 521)	Palbociclib + fulvestrant vs. placebo + fulvestrant	**Initial Report**			
		5.6 mo	9.2 mo (7.5-NR) vs. 3.8 mo (3.5-5.5); HzR, 0.42 (0.32-0.56); *P* <.001	—	10.4% (7.4-14.1) vs. 6.3% (3.2-11.0); *P* = 0.16
		Extended Follow-up			
		8.9 mo	9.5 mo (9.2-11.0) vs. 4.6 mo (3.5-5.6); HzR, 0.46; (0.36-0.59); *P* <.0001)	—	25% (19.6-30.2) vs. 11% (6.2-17.3)
		Extended Follow-up			
		44.8 mo	—	34.9 mo (28.8-40.0) vs. 28 mo (23.6-34.6); HzR, 0.81 (0.64-1.03); *P* = .09	—
MONALEESA-2: First-line for postmenopausal women (N = 668)	Ribociclib + letrozole vs. placebo + letrozole	**Initial Report**			
		15.3 mo	After 18 mo: 63.0% (54.6-70.3) vs. 42.2% (34.8-49.5)[b]	—	52.7% (46.6-58.9) vs. 37.1% (31.1-43.2); *P* <.001
		Extended Follow-up			
		26.4 mo	25.3 mo (23.0-30.3) vs. 16.0 mo (13.4-18.2); HzR, 0.568 (0.457-0.704); *P* = .0000000963	—	54.5% vs. 38.8%; *P* = .000254

(Continued)

Table 2. Summary of Phase III Clinical Trials of CDK4/6 Inhibitors (Cont.)

Study and Population	Treatment Arms	Median Follow-Up Duration	PFS (95% CI)	OS	ORR[a]
MONALEESA-3: 1st- or 2nd-line for postmenopausal women who progressed on ET (N = 726)	Ribociclib + fulvestrant vs. placebo + fulvestrant	**Initial Report**			
		20.5 mo	20.5 mo (19.5-23.5) vs. 12.8 mo (10.9-16.3); HzR, 0.593 (0.480-0.732); *P* <.001	—	40.9% vs. 28.7%; *P* = .003
		Extended Follow-up			
		42 mo	33.6 mo (27.1-41.3) vs. 19.2 mo (14.9-23.6)	57.8% (52.0-63.2) vs. 45.9% (36.9-54.5); HzR, 0.72 (0.57-0.92); *P* = .00455	—
MONALEESA-7: 1st-line for pre- or peri-menopausal women (N = 672)	Ribociclib + ET + goserelin vs. placebo + ET + goserelin	**Initial Report**			
		19.2 mo (IQR, 16.2-23.2)	23.8 mo (19.2-NR) vs. 13.0 mo (11.0-16.4); HzR, 0.55 (0.44-0.69); *P* <.0001	—	51% (45.0-57.0) vs. 36% (31.0-42.0); *P* = .00032
		Extended Follow-up			
		34.6 mo	—	70.2% (63.5-76.0) vs. 46.0% (32.0-58.9)[c]; HzR, 0.71 (0.54-0.95); *P* = .00973	—
MONARCH-2: 2nd-line for pre-, peri-, or postmenopausal women who progressed on ET (N = 669)	Abemaciclib + fulvestrant vs. placebo + fulvestrant	**Initial Report**			
		19.5 mo	16.4 mo vs. 9.3 mo; HzR, 0.553 (0.449-0.681); *P* <.001	—	48.1% (42.6-53.6) vs. 21.3% (15.1-27.6); *P* <.001
		Extended Follow-up			
		47.7 mo	16.9 mo vs. 9.3 mo; HzR, 0.536 (0.445-0.645); *P* <.001	46.7 mo vs. 37.3 mo; HzR, 0.757 (0.606-0.945); *P* = .01	—
MONARCH-3: 1st-line for postmenopausal women (N = 493)	Abemaciclib + ET vs. placebo + ET	**Initial Report**			
		17.8 mo	NR vs. 14.7 mo; HzR, 0.54 (0.41-0.72); *P* = .00021	—	59.2% (53.3-65.1) vs. 43.8% (35.5-52.4); *P* = .004
		Extended Follow-up			
		26.7 mo	28.2 mo vs. 14.8 mo; HzR, 0.54 (0.41-0.70); *P* = .000002	—	61.0% (55.2-66.9) vs. 45.5% (37.0-53.9); *P* = .003

[a] Measurable disease population. [b] Rate of locally assessed PFS. [c] Estimated OS at 42 mo.
CDK: cyclin-dependent kinase; ET: endocrine therapy; HzR: hazard ratio; IQR: interquartile range; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.
Source: References 10-25.

Side effects of CDK 4/6 inhibitors

Table 3. Adverse Events Associated With CDK4/6 Inhibitors

Adverse Event	Palbociclib		Ribociclib		Abemaciclib	
	All grades[a]	Grades 3-4[a]	All grades[a]	Grades 3-4[a]	All grades[a]	Grades 3-4[a]
Neutropenia	78.8-84.1	62.0-69.9	69.6-77.3	53.4-63.5	41.3-49.7	21.1-29.7
Leukopenia	39.0-60.0	24.8-38.3	28.4-34.9	14.1-21.3	20.8-33.1	7.6-11.1
Fatigue	37.4-44.1	1.8-2.6	23.6-41.3	1.2-3.0	39.9-42.9	1.8-4.1
Nausea	29.0-37.2	0.0-0.6	31.6-53.3	0.6-2.4	38.5-49.2	0.9-2.7
Infection	25.2[b]-62.6	0.3[c]-7.4	26.0[d]-57.8	1.0[d]-7.7	28.6[b]-42.6	0.9[b]-6.6
Anemia	24.1-31.6	2.6-5.8	17.2-22.4	1.2-3.9	28.4-34.7	5.8-9.0
Headache	21.2-28.7	0.2-0.9	21.5-26.9	0.0-0.3	15.6-24.0	0.6-0.9
Diarrhea	19.2-28.4	0.0-1.4	20.3-38.3	0.6-2.4	81.3-87.1	9.5-14.5
Constipation	16.8-22.0	0.0-0.5	16.4-27.8	0.0	13.6-17.4	0.6-0.7
Asthenia	16.9-18.0	2.3-2.7	12.8	0.6	NR	NR
Thrombocytopenia	15.5-25.5	1.6-2.9	5.5-9.3	0.6-1.0	15.6-17.5	3.4
Alopecia	14.8-33.6	NA	18.6-34.4	NA	15.6-27.5	NA
Vomiting	14.5-21.7	0.3-0.9	19.1-33.5	1.4-3.6	25.9-30.3	0.9-1.5
Rash	14.5-19.8	0.6-0.9	13.1-22.2	0.3-1.5	11.1-15.3	0.9-1.1
Nasopharyngitis	14.0	0.0	NR	NR	NR	NR
Arthralgia	13.0-37.6	0.3-0.9	24.0-33.2	0.6-0.9	11.6-17.4	0.0-0.7
Decreased appetite	12.8-17.4	0.7-1.2	9.0-20.7	0.2-1.5	26.3-28.8	1.1-1.5
Blood creatinine elevation	NR	NR	NR	NR	11.8-20.5	0.9-2.1
Stomatitis	11.6-31.5	0.2-1.1	10.1	0.6	15.2-17.5	0.4-0.5
Fall	11.3	0.7	NR	NR	NR	NR
Dyspnea	10.7-16.4	0.3-1.4	1.2-6.3	1.2	10.9-12.0	2.7
Pyrexia	10.7-13.6	0.0-0.3	15.2	0.6	10.9-13.4	0.7
Peripheral edema	10.4-12.8	0.0	5.7	0.3	11.6-14.1	0.0
Myalgia	10.1-14.2	0.0-0.2	10.1	0.0	NR	NR
Dysgeusia	10.1-11.6	0.0-0.3	NR	NR	17.9-18.6	NR
Muscle spasms	10.1	0.0	NR	NR	NR	NR
Abdominal pain	7.2-13.3	0.6-1.4	10.1	0.6	29.1-37.2	1.2-3.2
Musculoskeletal pain	7.2-12.5	0.2-0.3	NR	NR	NR	NR
AST elevation	4.3-11.6	2.6-3.2	11.9-36.7	3.6-5.7	12.2-16.8	2.3-3.7
ALT elevation	3.8-12.6	1.7-2.7	12.8-47.6	5.4-9.3	13.4-17.4	4.1-6.4
Pneumonia	0.9	0.3	0.9	0.3-1.9	NR	NR
QT prolongation	0.0	0.3	2.7-12.5	1.2-1.8	NR	NR
VTEs	NR	NR	NR	NR	6.1	0.0
ILD	NR	NR	0.3-1.2	0.0-0.2	NR	NR
≥1 dose reduction for AE	36.0-54.2	NR	33.1-54.5	NR	43.4-46.5	NR
Discontinuation for AE	2.6-12.2	NR	3.6-8.1	NR	9.5-19.6	NR

[a] Percentage. [b] Includes URTI and urinary tract infection. [c] Includes URTI. [d] Includes URTI and viral URTI. AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CDK: cyclin-dependent kinase; ILD: interstitial lung disease; NA: not applicable; NR: not reported; URTI: upper respiratory tract infection; VTE: venous thromboembolic event. Source: References 10-25.

Immunotherapy – Keynote 522

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

Cortes J et al. DOI: 10.1056/NEJMoa2202809

CLINICAL PROBLEM

In an interim analysis in the KEYNOTE-355 trial, pembrolizumab plus chemotherapy resulted in longer progression-free survival than chemotherapy alone among patients with advanced triple-negative breast cancer whose tumors expressed a programmed death ligand 1 (PD-L1) combined positive score (CPS; the number of PD-L1–staining tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100) of 10 or more. Results from the final analysis of overall survival are needed.

CLINICAL TRIAL

Design: The international phase 3, double-blind, randomized, placebo-controlled KEYNOTE-355 trial examined the efficacy and safety of pembrolizumab plus chemotherapy among patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer.

Intervention: 847 patients were assigned in a 2:1 ratio to receive pembrolizumab (200 mg every 3 weeks for up to 35 infusions) plus chemotherapy or placebo plus chemotherapy. Primary end points included overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (CPS-10 subgroup), among those whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 subgroup), and in the intention-to-treat population.

RESULTS

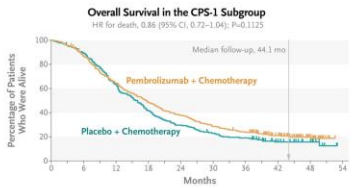
Efficacy: Overall survival was significantly longer with pembrolizumab–chemotherapy than with chemotherapy alone in the CPS-10 subgroup. In the CPS-1 subgroup, the between-group difference was not significant; significance was not assessed in the intention-to-treat population.

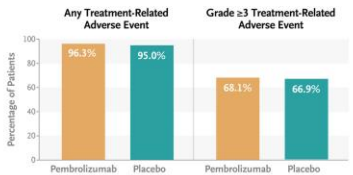
Safety: The incidence of any adverse event related to the trial regimen was similar in the two trial groups; anemia, neutropenia, and nausea were most common. The incidence of adverse events of grade 3, 4, or 5 was also similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- The benefit of pembrolizumab was observed with both paclitaxel-based and nanoparticle albumin-bound paclitaxel–based chemotherapy, but the small number of patients who received paclitaxel precludes firm conclusions.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

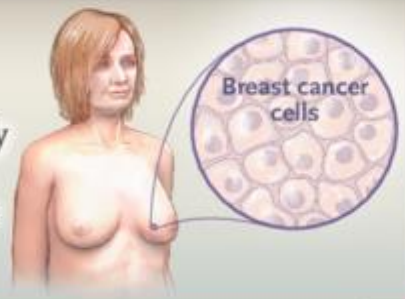
Among patients with previously untreated advanced triple-negative breast cancer and PD-L1 expression scores of 10 or more, pembrolizumab plus chemotherapy resulted in longer overall survival than chemotherapy alone, and no new safety signals emerged.

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

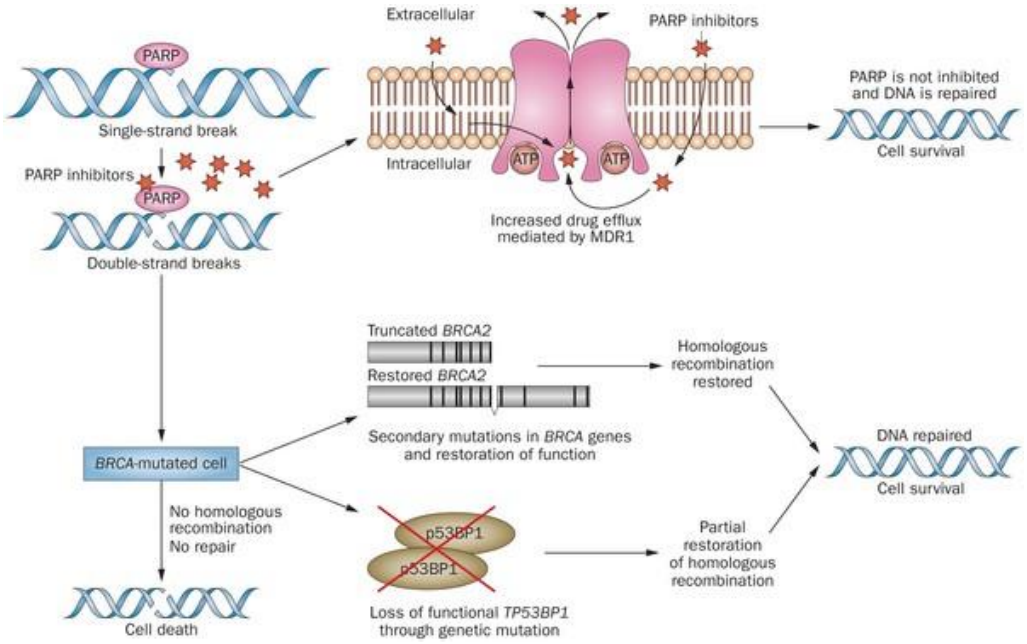
1174 Patients with previously untreated triple-negative breast cancer



	Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784)	Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo (N=390)
Pathological complete response at time of surgery	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

P. Schmid et al. 10.1056/NEJMoa1910549

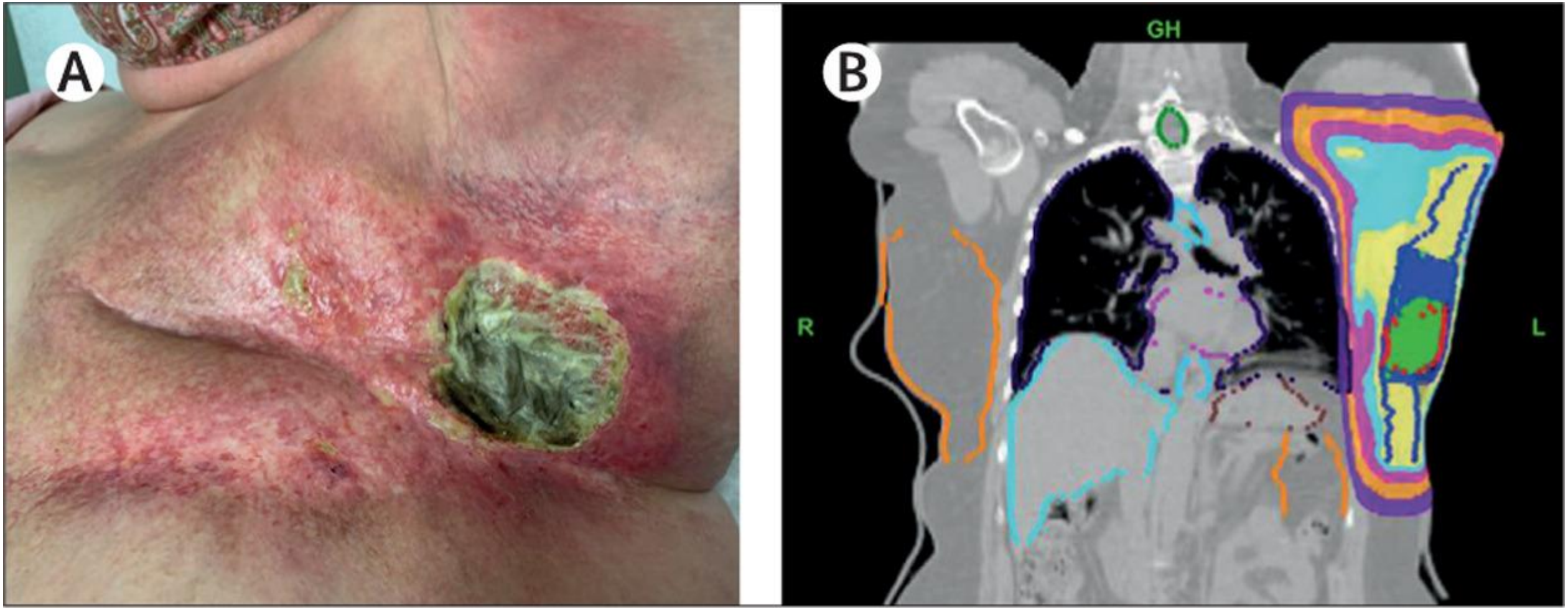
Adjuvant Systemic Therapy



Tutt ANJ, et al. N Engl J Med. 2021 Jun 24;384(25):2394-2405.

Adjuvant Radiation Therapy

- Painless
- Hypofractionation protocol (3-4 weeks)
- Standard protocol with nodal disease (6 weeks)
- Side effects: fatigue, burn that resolves w/treatment
- **Component of BCT**
- Post-mastectomy radiation therapy=PMRT
  - Indications: T3 (> 5cm), ≥ 4 nodes, close or + margins
  - Newest consensus statement: T1-T2 cancer with 1-3 positive nodes may benefit from radiation after mastectomy


A
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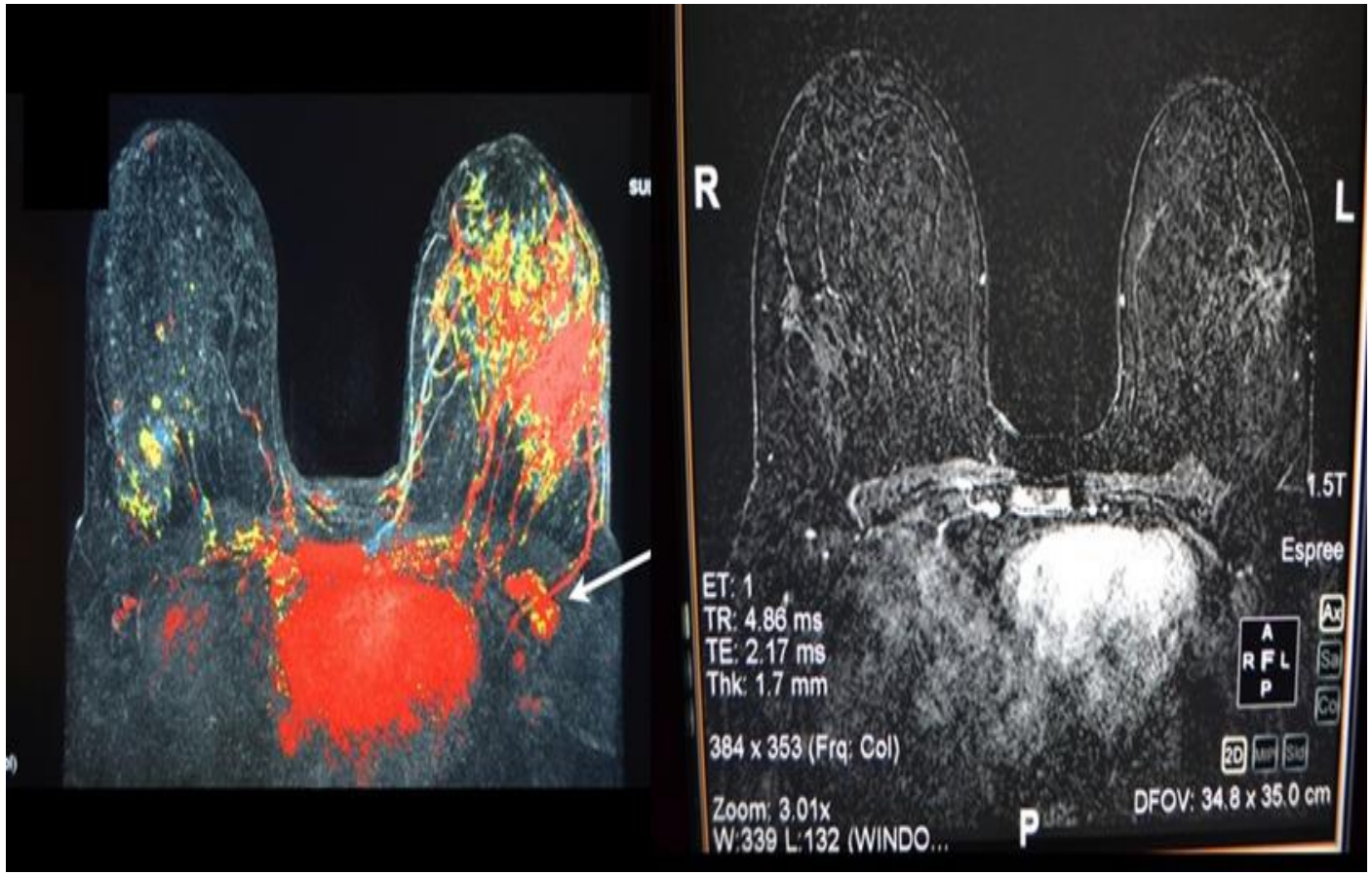
Future Directions

- Alliance A11202/NSABP B51 – ongoing trial…can we avoid axillary dissection despite metastatic lymph nodes after neoadjuvant chemotherapy?
- NRG B005 – awaiting results…can we avoid surgery altogether in patients who are exceptional responders after neoadjuvant chemotherapy?
- COMET/LORD/LORIS – ongoing trial…avoiding surgery on patients with DCIS



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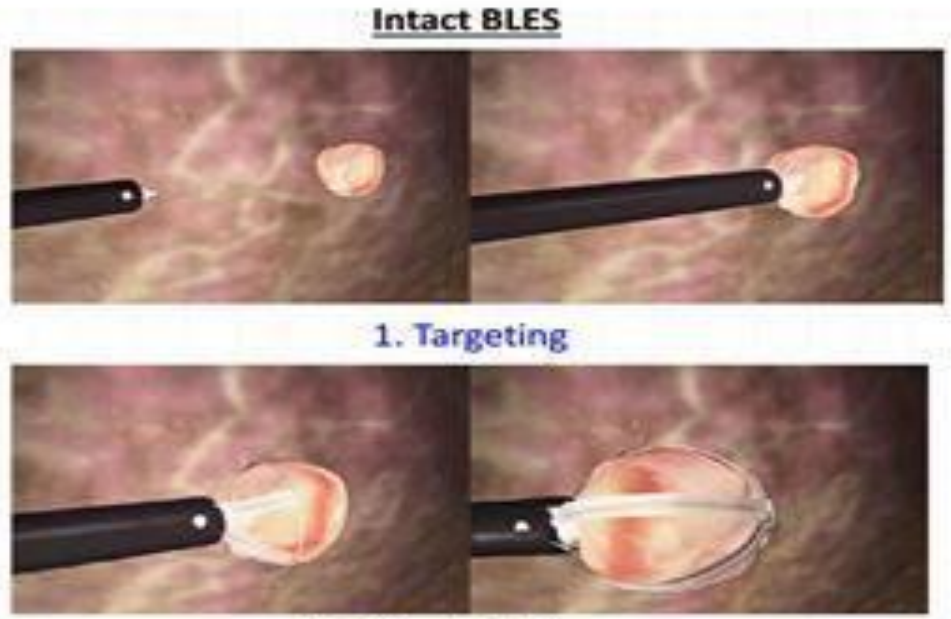
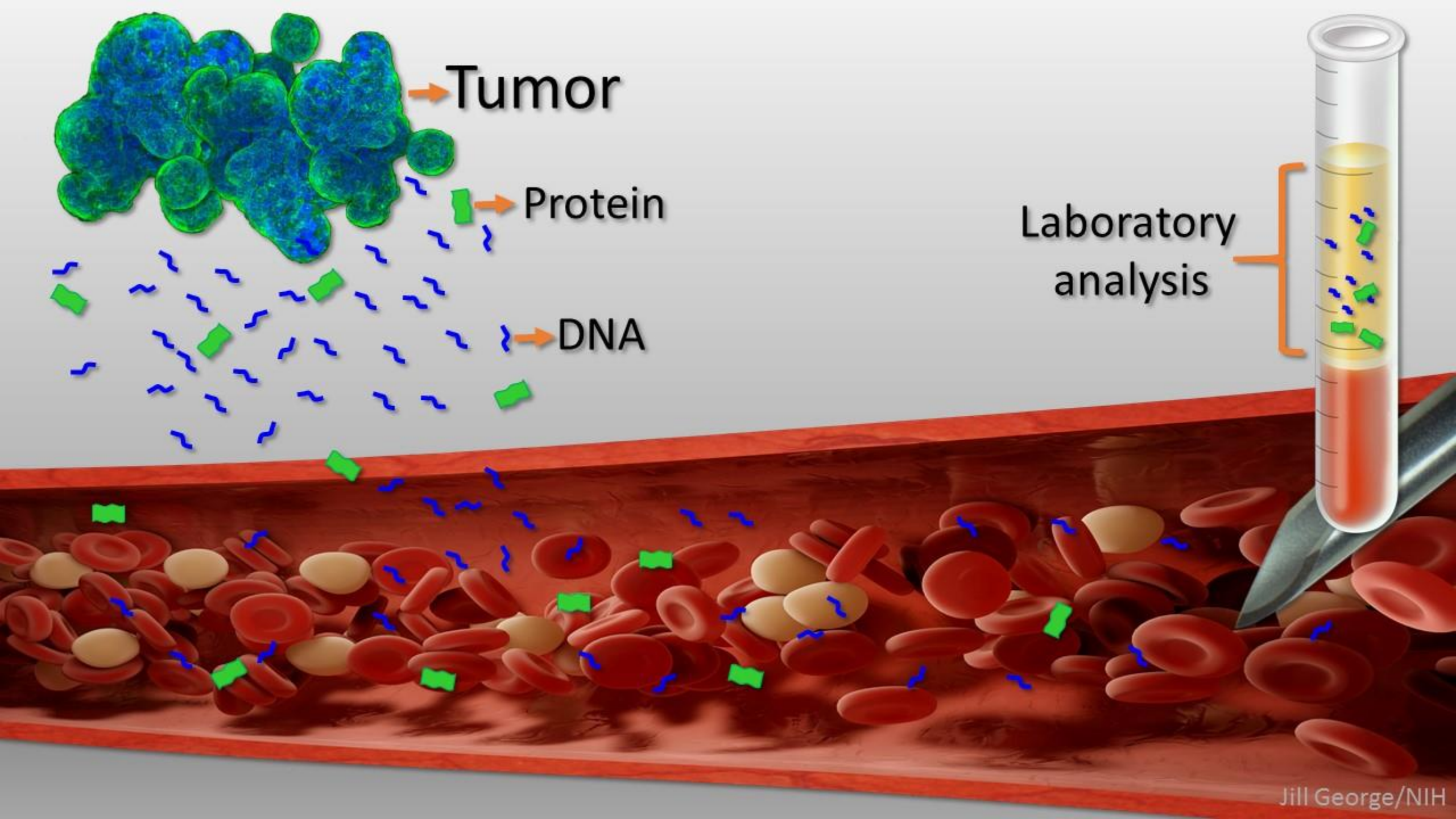


Yao, K. Ann Surg Oncol 26, 933–935 (2019)

Cryotherapy

Simmons, et al. Ann Surg Oncol (2016) 23: 2438.


Tumor
Protein
DNA
Laboratory analysis
Jill George/NIH

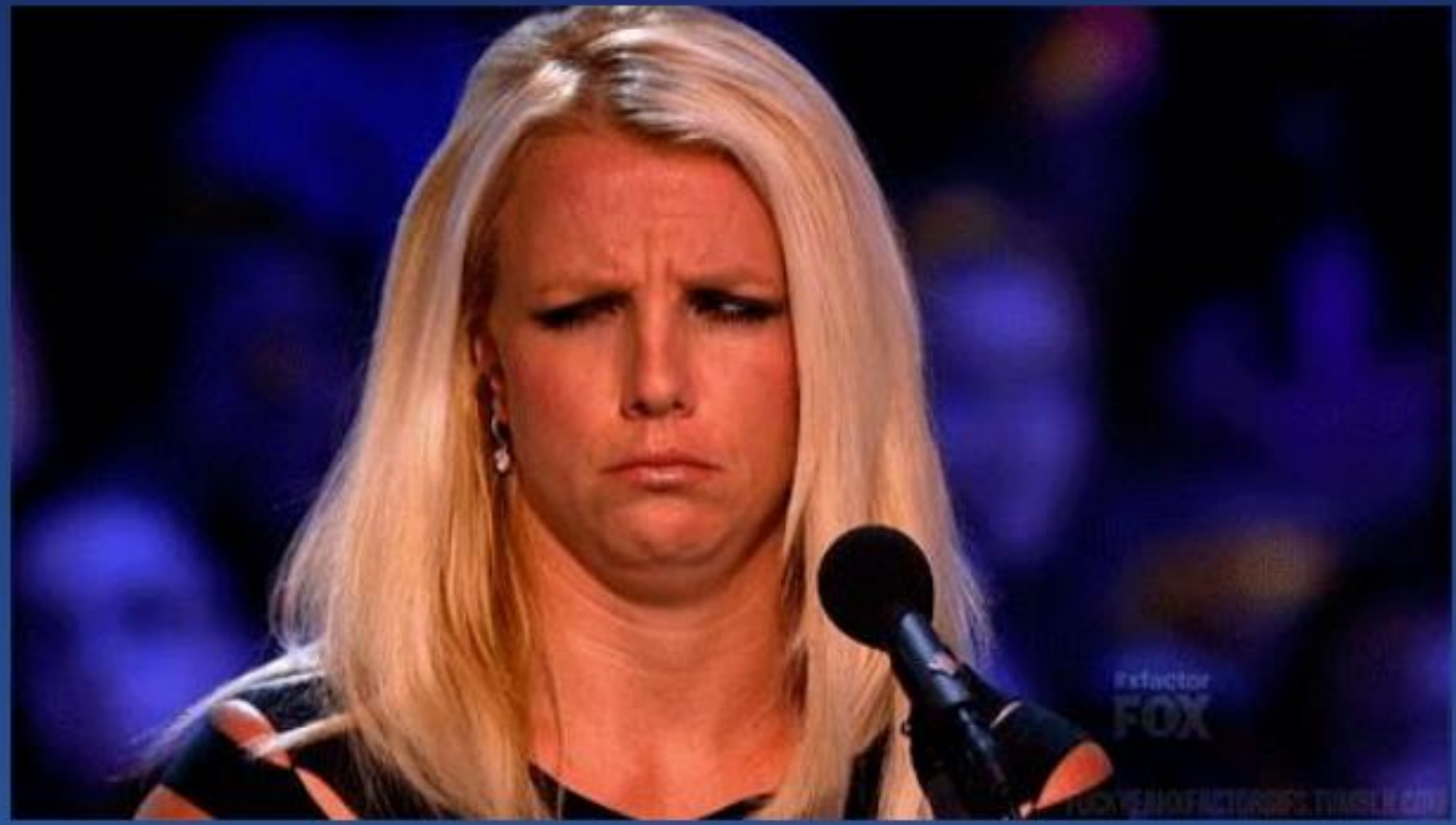
Vaccines

On December 21, 2020, the FDA approved an investigational drug application for a triple-negative breast cancer vaccine.

Conclusions

- Improved breast cancer detection and treatments have led to improved outcomes.
- Biology of breast cancer is the primary driver of treatments and outcomes.
- Novel drugs and innovations have led to better overall survival and quality of life.
- Traditional dogmas continue to be challenged with results from clinical trials.

CLEAR AS MUD!




thank you
danke
謝謝
ngiyabonga
شكراً جزيلاً
рахмат
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Баярлалаа
спасибо
dank je
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