Breast cancer

Breast Cancer:
Overview
Prevention, Diagnosis, Treatment

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NIH NATIONAL CANCER INSTITUTE

TRACO Lecture
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Breast cancer

Breast anatomy

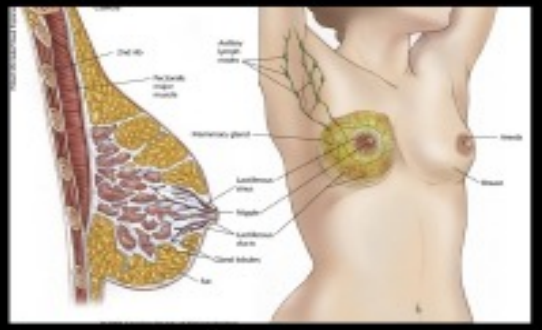
Breast Anatomy

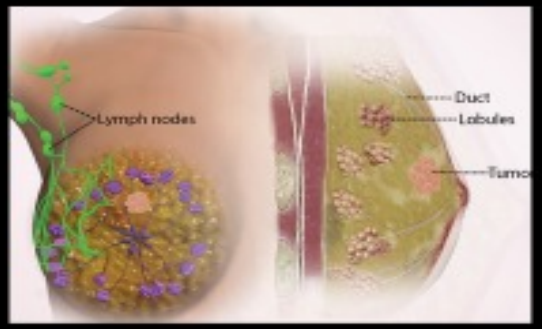
Embedded within fatty and fibrous tissue:

- 15-20 glands (lobes) which
- which each have
- smaller lobules that
- produce milk. They are
- inter-connected by ducts
- that carry the milk to the
- nipple.

Breast Cancer develops in the breast cells and progresses in stage

- **About 90% of all breast cancers start in the ducts or lobes of the breast**





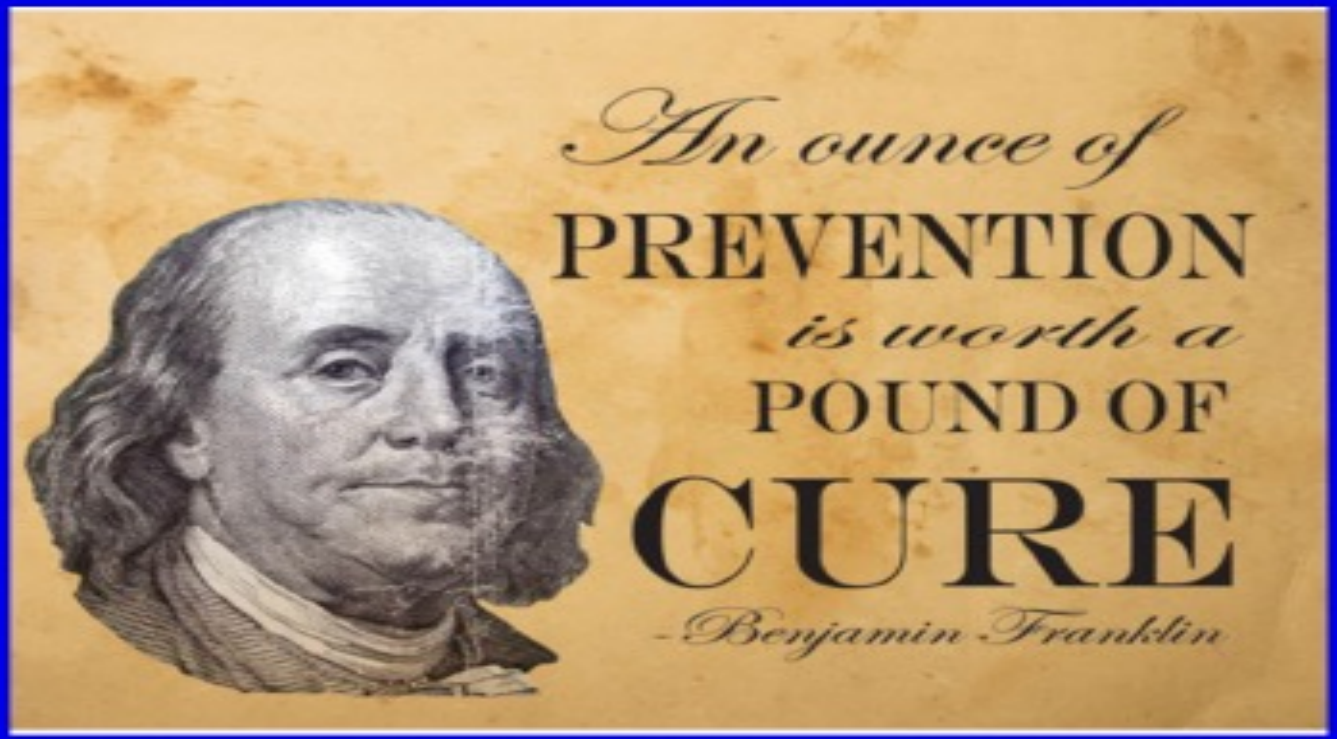
Breast Cancer

- *Precise* reasons why a woman develops breast cancer are difficult to specify.
- Genetic + environmental + lifestyle factors
- Hormones seem to have an important role. Research has shown a link between estrogen levels and the risk of developing *HR+ breast cancers.*

Known Breast Ca Risk Factors

- Age (80% of breast cancers occur after menopause)
  1/8 → age < 45
  2/3 → age ≥ 55
- History of Prior breast cancer
  3- 4 X more likely to develop a new cancer (same or other breast)
- History of benign breast conditions with atypia (4X Risk) or without (2X Risk).
- Exposure to excess endogenous or exogenous hormones:
  1. Early menarche
  2. Late menopause
  3. Use of Hormone Replacement Therapy
  4. No pregnancies or age >35 at birth of first child
- Radiation exposure before age 40
  (breast ca after xrt for Hodgkin's lymphoma)
- Dense breast tissue on mammogram
  glands > fat
- lifestyle factors (alcohol [↑ estrogen, DNA damage], lack of exercise [exercise consumes blood sugar and limits IGF, a hormone that can effect breast cell growth], also obesity ➤ (BMI > 25) ➤ extra fat cells = more estrogen in the body.

Prevention


An ounce of
PREVENTION
is worth a
POUND OF
CURE
-Benjamin Franklin

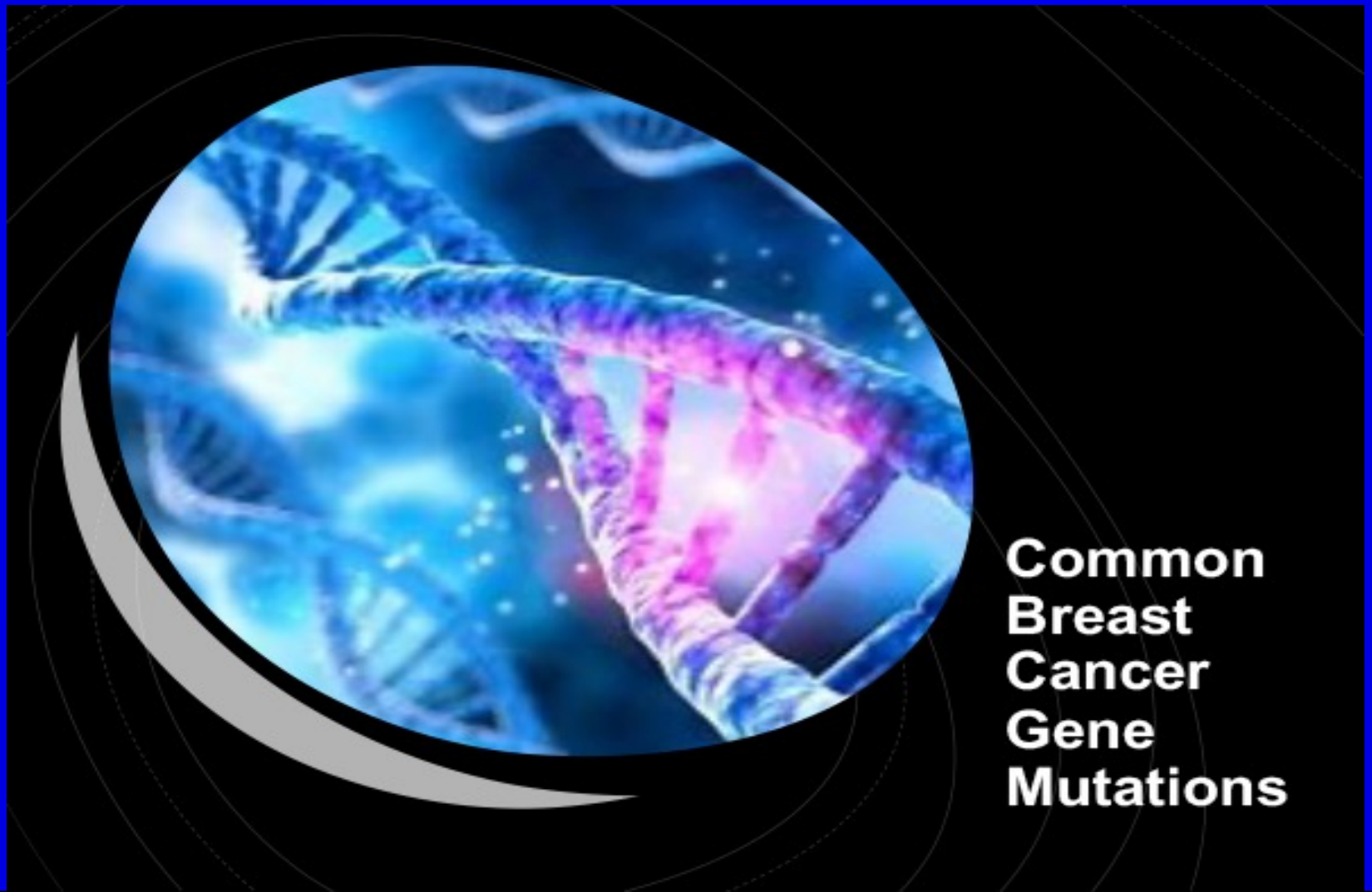
Prevention

Breast Cancer Prevention

Breast Cancer Prevention Starts with Healthy Habits.
Some risk factors, such as family history, can't be changed.
However, there are lifestyle factors that can lower your risk.

1. **Limit Alcohol** – even small amounts increase risk. In fact, risk is directly proportional to the amount of alcohol intake, and not the type of alcohol
2. **Maintain a Healthy Weight**
3. **Be Physically Active**
4. **Breast Feed** – the longer you breast feed, the greater the protective effect
5. **Limit Post-Menopausal Hormone Therapy** – preferable to manage symptoms with non-hormonal therapies and medications.
6. **Eat a Healthy Diet** – women who eat a Mediterranean diet supplemented with extra-virgin olive oil and mixed nuts might have a reduced risk of breast cancer. The Mediterranean diet focuses mainly on plant-based foods, such as fruits and vegetables, whole grains, legumes, and nuts, along with fish and chicken.
7. **Contraception**: There is some evidence that hormonal contraception increase the risk of breast cancer, but the risk is small, and begins to decrease as soon as you stop. A recent study determined that one additional breast cancer could be expected for every 7,960 women who use hormonal contraception for at least 1 yr

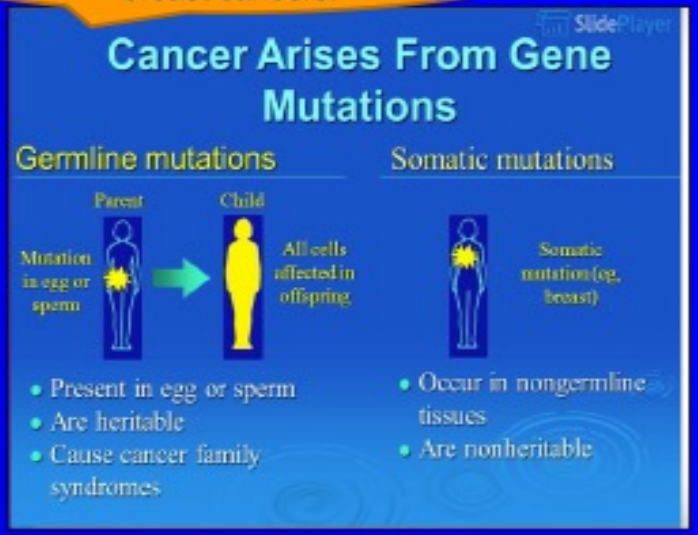
GENES



Mutations

Germline VS Somatic Mutations

Inherited Genetic Mutations Account for ≅ 5-10% of all breast cancers!

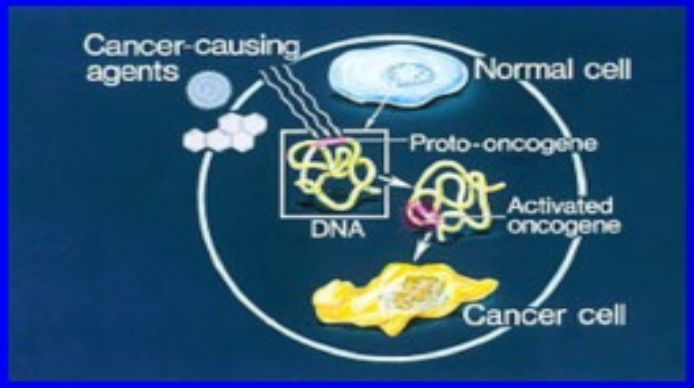


- Many mutations, such as those found in the BRCA1 and BRCA 2 genes, are passed down in an autosomal dominant pattern.
- 1 bad gene from 1 parent = increased risk

- Somatic Mutations: **Majority of Breast Cancers**

Changes in DNA over lifetime

- Environmental Exposures
- Natural aging process



Genes

BRCA 1 and BRCA 2 Genes

- Produce proteins that help repair damaged DNA
- Everyone has two copies of each gene, one copy inherited from each parent, and those who inherit harmful variants in one of these genes, have increased risks of several cancers, as well as the tendency to develop cancer at a younger age.
- It is the most common cause of hereditary breast cancer, accounting for up to 10% of all diagnoses.
- BRCA mutations also raise women's chances for ovarian cancer and other cancers caused by the same cells (fallopian tube cancer and primary peritoneal cancer), and, in men, prostate cancer as well as male breast cancer. Finally, both men and women with either mutation are at risk of pancreatic cancer, although the risk increase in low.
- Women with either of these mutations have up to a 72% chance of breast cancer during their lifetime; however, the risk for any one woman depends on a number of factors, including lifestyle and other environmental risks.

CHK2 Gene (Checkpoint Kinase 2)

- Codes a protein which is activated when there is DNA damage
- It is a heritable mutation that can double the lifetime risk of breast ca

Genes

PALB2 Gene

- Codes a protein that helps the BRCA2 protein repair damaged DNA.
- Some studies suggest that women with a PALB2 mutation have a 14% chance of developing breast cancer by age 50 and a 35% chance by age 70.

PIK3CA Gene

- Gives instructions to other cells in the body to make PI3-Kinase, which is involved in the life cycle of the cell.
- When mutations result in an altered protein which is not properly functional, cells may grow and divide abnormally.
- The mutation first occurs during embryo development, or the early stages of pregnancy, meaning that it is not passed down from parents to children, and therefore is not a cause of hereditary breast cancer.
- PIK3CA mutations are found in about 30% - 40% of breast cancers

PTEN Gene

- Helps control cell growth
- An inherited mutation can cause "Cowden Syndrome" which puts one at risk for cancerous and non-cancerous breast tumors and other growths.
- Women with a PTEN mutation have a lifetime breast cancer risk of 25% - 50%

Genes

HER2 Gene

- Codes the human epidermal growth factor receptor 2 protein, which is found on the surface of all breast cells and is involved in normal cell growth.
- If the HER2 gene mutates to become "overexpressed" it tells cells to make too much HER2 protein, which causes the cells to grow out of control.
- HER2 is also not an inherited mutation, but rather a somatic mutation.
- Only about 10% - 20% of breast cancer cases are what we call "HER2 positive" meaning that there is a change in the HER2 gene that makes the breast cells grow out of control.
- This is a "targetable mutation" and there are effective treatments for HER2+ breast cancer
- Recently, studies in metastatic ER+ tumors suggest that some HER2 mutations emerge as a mechanism of acquired resistance to endocrine therapy.

TP53 Gene

- This is a tumor suppressor gene: it helps stop the growth of cells that have damaged DNA
- This mutation can be inherited and causes Li-Fraumeni syndrome, resulting in increased chances of not only breast cancer, but also – leukemia, brain tumors, and sarcomas.
- Women who have this syndrome have nearly a 100% chance of developing breast cancer in their lifetime, and a 50% chance of developing cancer before the age of 30

ATM Gene

- Helps repair damaged DNA
- Inheritance of one bad gene results in increased risk for breast and pancreatic ca
- Lifetime risk of developing breast cancer is 38%, and up to 69% with a specific mutation

Family history

Myth:

If I don't have a family history of breast cancer, I won't get it

Fact:

Most people diagnosed with breast cancer have no known family history

- Only 5-10% of breast cancers are believed to be hereditary
- The Vast majority are more likely due to environment and lifestyle
- As physicians, we often can't explain why one individual gets breast cancer and another does not.
- We do know that the biggest risk factors are simply being a woman, and aging
- Over time, healthy breast cells can develop mutations on their own, eventually turning into cancer cells.
- Regardless, if you have a strong family history on either of your parents side, this is an important risk factor and should be taken seriously.

Sisters

- The Sister Study is being conducted by the National Institute of Environmental Health Sciences
- From 2003-2009 more than 50,000 women across the U.S. and Puerto Rico, who were between the ages of 35-74 and whose sister had breast cancer, joined this landmark research effort in order to allow the investigation of causes of breast cancer.
- Because of their shared environment, genes, and experiences, studying sisters provides a greater chance of identifying avoidable risk factors that would help to prevent breast cancer.
- The sister study is currently tracking the health of women in the cohort.
  - participants complete health updates annually, as well as detailed questionnaires every 2-3 years.
- Research in the Sister Study focuses on causes of breast cancer, and other health issues in women, as well as on factors that influence quality of life and outcomes after a breast cancer diagnosis.

Behaviors

Myth:

If I maintain a healthy weight, exercise regularly, eat healthy, and limit alcohol, I won't have to worry about breast cancer.

Fact:

Although these behaviors can help lower breast cancer risk, they can't eliminate it.

- "I eat healthy, I exercise, I am not overweight, I limit my alcohol intake, so doctor, how did I get breast cancer?"
- Please understand, and help your friends and family to understand – that even though you think you are doing everything right, no one is 100% safe.

Breast cancer statistics

Female Breast Cancer Stat Facts

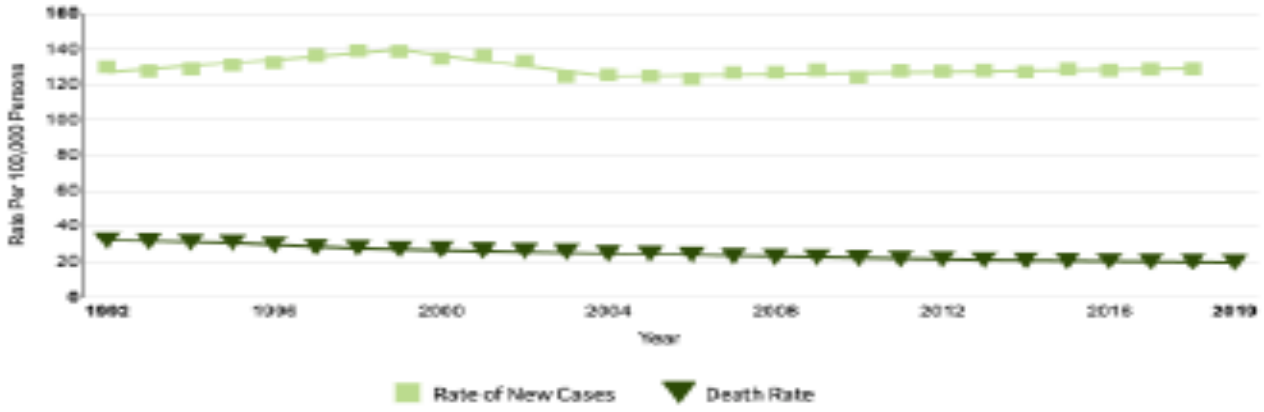
At a Glance

Estimated New Cases in 2021	281,550
% of All New Cancer Cases	14.8%
Estimated Deaths in 2021	43,600
% of All Cancer Deaths	7.2%

5-Year Relative Survival

90.3%

2011–2017



New cases come from SEER 13. Deaths come from U.S. Mortality.
All Races, Females. Rates are Age-Adjusted.

- Estimates of new cases and deaths for 2021 are projections made by the American Cancer Society, based on earlier reported data.

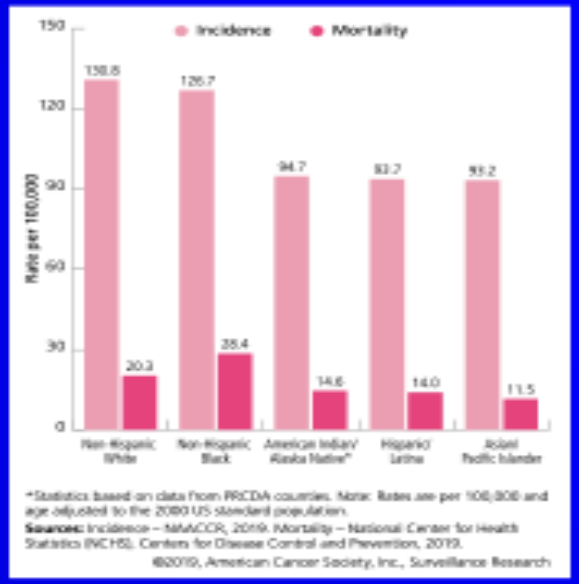
MEN:

- Lifetime Risk: 1 in 833
- About 2,650 new cases of invasive disease are projected to be diagnosed in 2021

Statistics

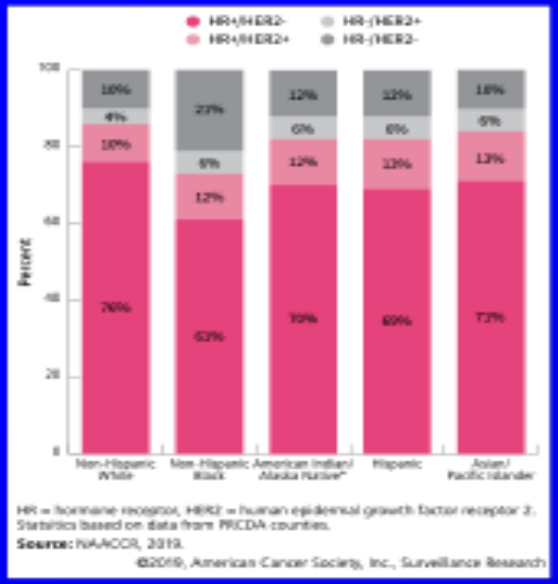
Statistics

Incidence & Mortality By Race/Ethnicity (2013-2017)



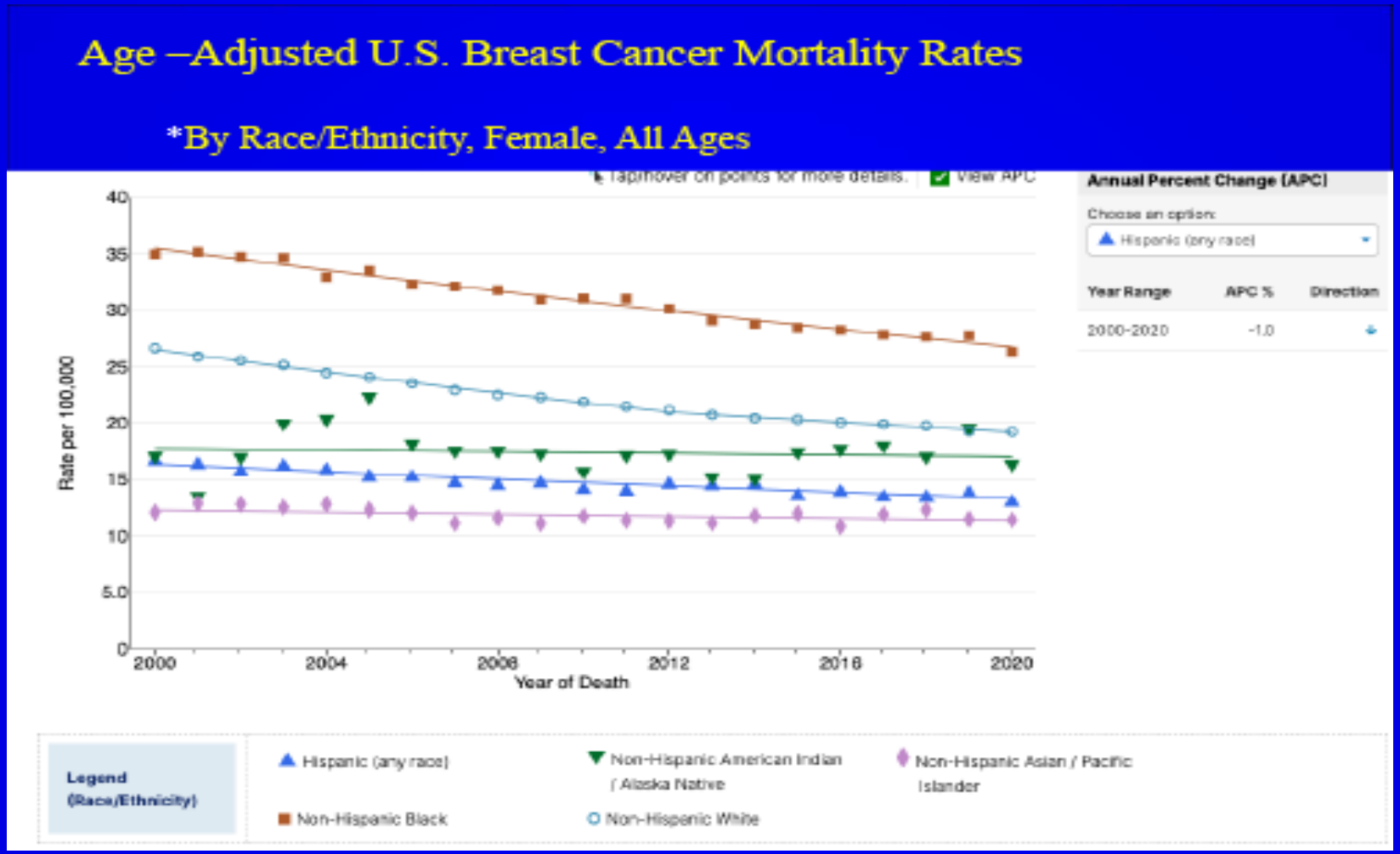
*Statistics based on data from PRCDA counties. Note: Rates are per 100,000 and age-adjusted to the 2000 US standard population.
Sources: Incidence – NAACCR, 2019. Mortality – National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2019.
©2019, American Cancer Society, Inc., Surveillance Research

Distribution of Cancer Subtypes by Race/Ethnicity (2012-2016)



HR = hormone receptor, HER2 = human epidermal growth factor receptor 2. Statistics based on data from PRCDA counties.
Source: NAACCR, 2019.
©2019, American Cancer Society, Inc., Surveillance Research

Age-adjusted mortality



Early Detection

Breast lump

Myth:

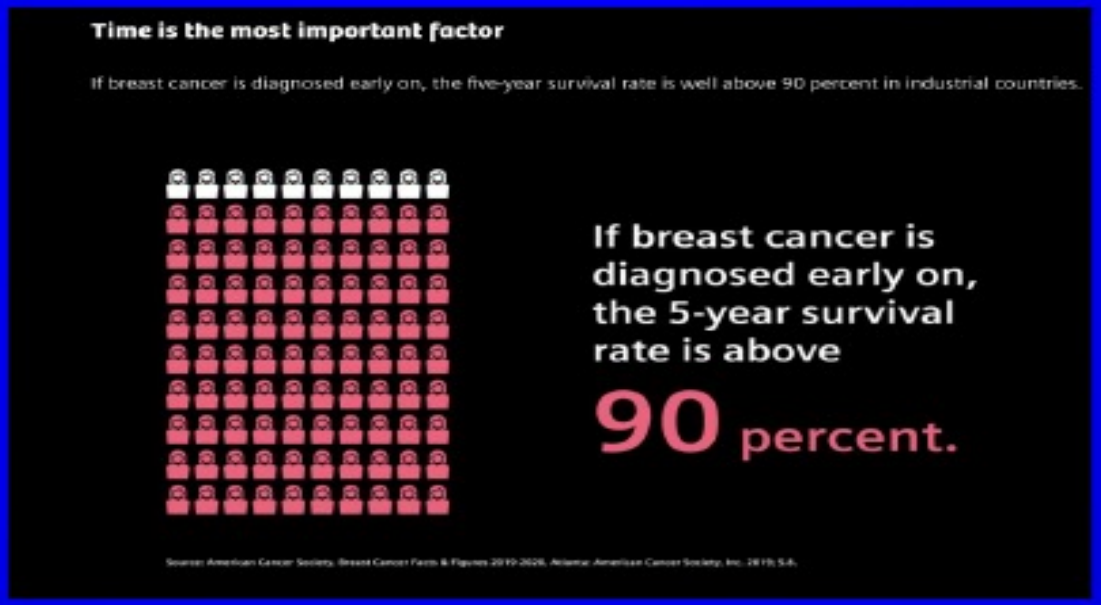
Breast cancer always causes a lump you can feel

Fact:

Breast Cancer might not cause a lump, especially when it first develops.

- People are sometimes under the impression that breast cancer always causes a lump that can be felt during a self – exam.
- They might use this as a reason to skip mammograms, thinking that they would be able to feel any change that might indicate a problem.
- If a lump is felt, it is possible that the cancer might have already moved beyond the breast into the lymph nodes.

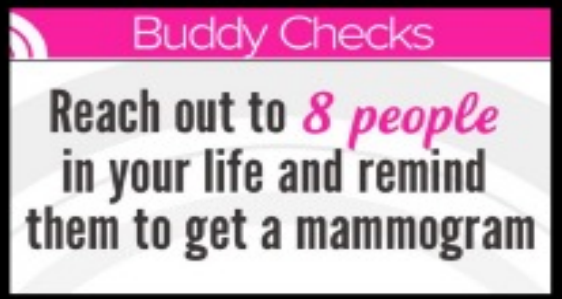
Early detection



Mammograms

- Mammograms can be used as screening tools to detect early breast cancer in women experiencing no symptoms
- Mammograms can also be used to detect and diagnose breast disease in women experiencing symptoms such as a lump, pain, or nipple discharge.
- Reduces mortality by:
  - 26% aged 50-74
  - 17% aged 40-49

*American Cancer Society



3 types of mammograms

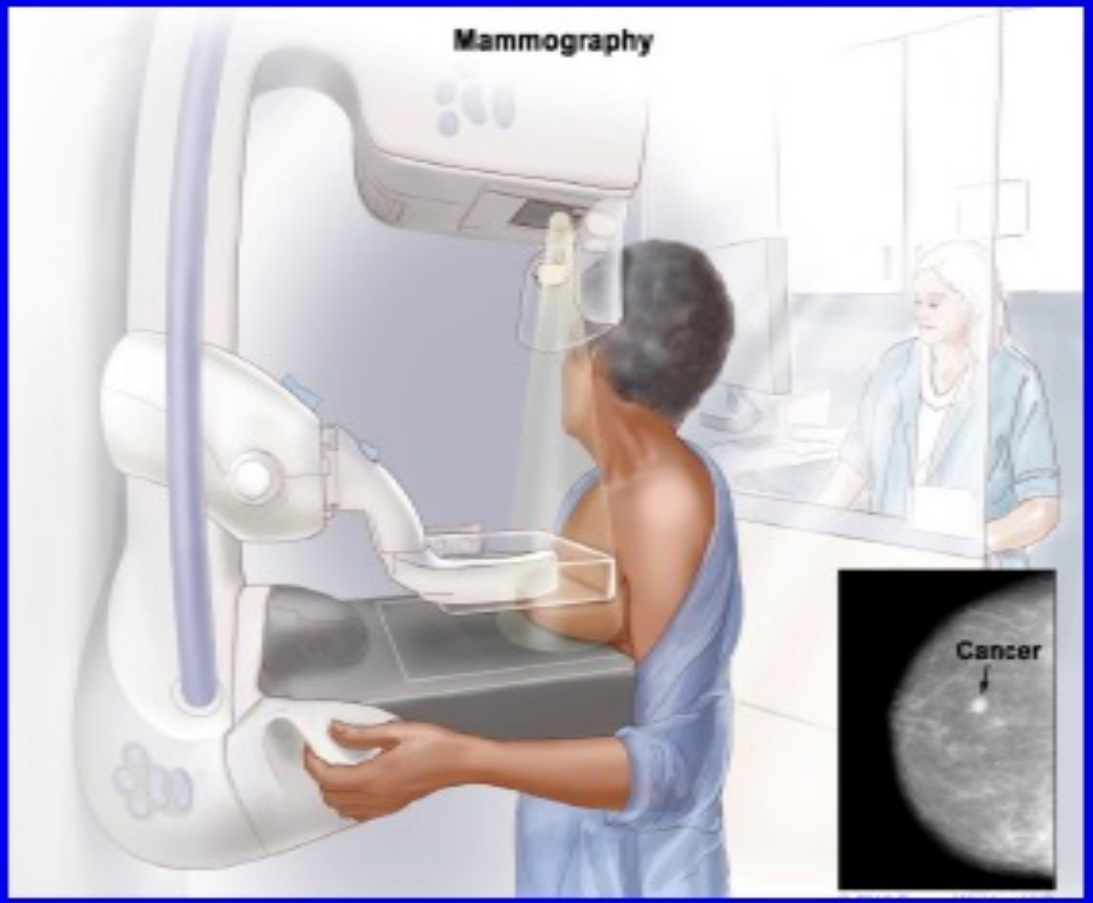
3 Types of Mammograms

1. Film Mammography
   - X-Ray Picture of the breast
   - Antiquated Method!

2. Digital Mammography
   - Computer Picture of the breast

3. Digital Breast Tomosynthesis (DBT)
   - uses x-rays to take a series of pictures of the breast from many different angles. Then, a computer is used to make 3-D pictures of the breast

Approved by the FDA in 2018 & now in use in 3 out of 4 facilities. One study found that DBT reduced false positive results. Studies are on-going comparing digital mammography to DBT.



American Cancer Society Guidelines for the Early Detection of Breast Cancer

American Cancer Society Guidelines for the Early Detection of Breast Cancer

Average Risk

- **Age 40-44**: women have the **choice** to begin annual mammograms. Risks and benefits should be considered.
- **Age 45-54**: **annual** mammograms are recommended.
- **Age 55 and older**: switch to **biannual** mammograms, or have the choice to continue an annual schedule based on risks/benefits.

Screening should continue as long as a woman is in good health, and life expectancy is 10 years or more.

High Risk

Annual MRI + Mammogram ***(as long as a woman is in good health and life expectancy is >/= 10 years)***

- Lifetime risk of breast cancer:
  >/= 20-25%
  - using risk-assessment tools (based mainly on family history)
- Known BRCA 1 or BRCA 2 Gene Mutation.
- First degree relative with BRCA 1 or BRCA 2 gene mutation
- Chest Radiation ages 10-30

MRI

American Cancer Society Guidelines:
Use of MRI For Early Detection of Breast Cancer

- MRI uses a magnet, radio waves, and a computer to make a series of detailed pictures, and does not utilize radiation.
- While MRI is more sensitive than mammogram, it also has a higher false positive rate. This may lead to unnecessary biopsies and other procedures.
- The American Cancer Society recommends *against* use of MRI for women whose lifetime risk of breast cancer is < 15%.
- For women who have a moderately increased lifetime risk of breast cancer (15-20%) there is not enough evidence to make a recommendation for or against use of annual MRI.
- If MRI is used, it should be in addition to, and not in place of a screening mammogram, given that it can miss cancers that a mammogram would find.

American Cancer Society Guidelines for the Early Detection of Breast Cancer

Clinical Breast Exam & Breast Self Exam:

- There is no solid clinical trial evidence that a physical breast exam done either by a health care professional or by the women themselves, provides any clear benefit in early detection or reducing breast cancer mortality.
- Due to this lack of evidence, regular clinical breast exams and breast self exams are not part of the ACS guidelines.
- However, all women should be familiar with how their breast look and feel, and report any changes to their physician ASAP.

Self Breast Exam

Self Breast Exam (SBE)

- Size
- Shape
- Color
- Dimpling
- Puckering
- Retraction
- Thickening
- Inverted nipple
- Nipple discharge

Step 1

Shoulders straight, arms on hips

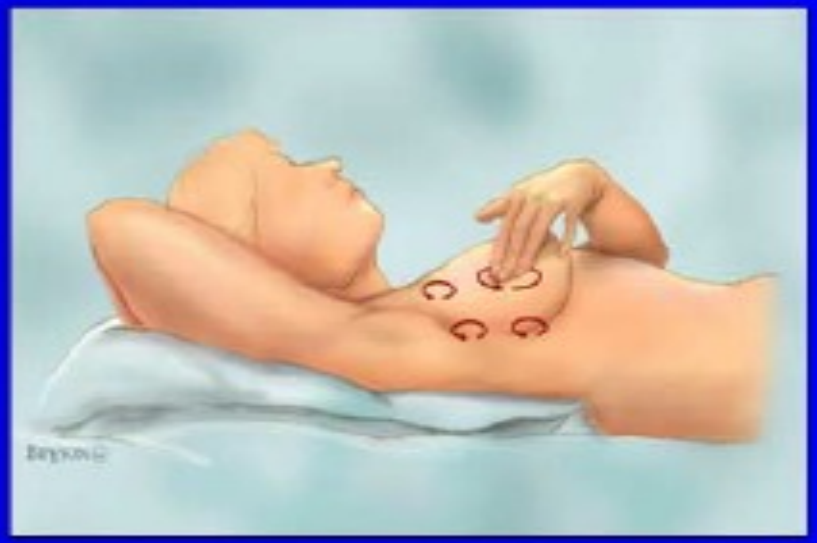
Step 2

Arms over head

Self Breast Exam

Self Breast Exam

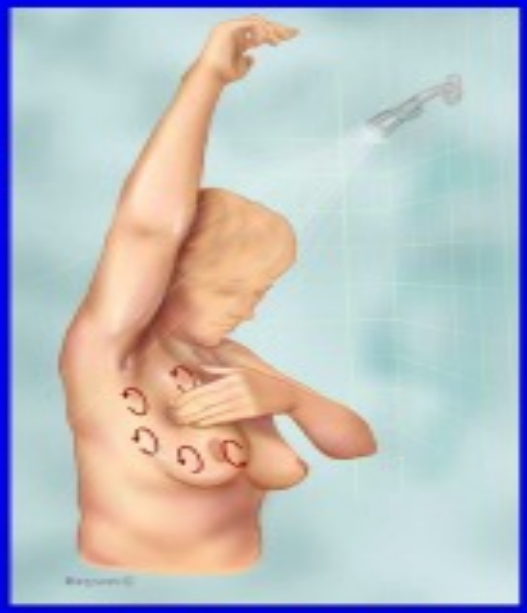
Step 3



Examine lying down

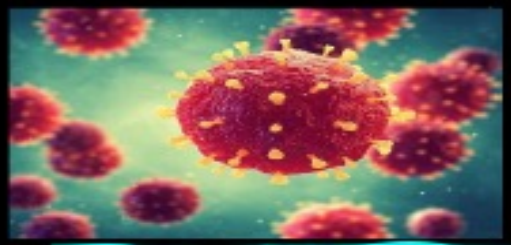
- Firm, smooth touch
- Fingers flat & together
- Circular Motion
- Follow a pattern
- Cover whole breast

Step 4



Examine upright

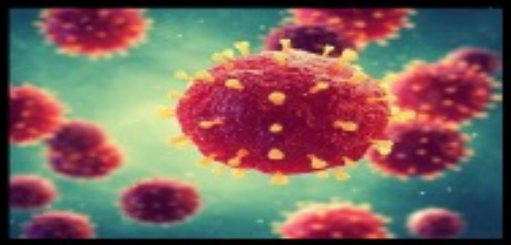
COVID-19



COVID-19

- The COVID – 19 pandemic has had profound impact on cancer care, with overall cancer deaths rising.
- Delays in breast cancer screening, prevention, and treatment were likely the cause of some of the increase in breast cancer related deaths
  (Kuderer et al Lancet June 20, 2020).
- Interestingly, the COVID pandemic magnified racial and ethnic differences.
- A recently published study that utilized qualitative interviews with black women revealed that low levels of mammogram screening during the pandemic resulted from barriers such as poverty, lack of health insurance, medical mistrust, limitations in resources, and overall negative healthcare experiences
  (Bea et al J Racial and Ethnic Health Disparities, May 2022).
- Using data from the Breast Cancer Surveillance Consortium,Sprague et al **(JNCI, 2021)** noted racial and ethnic differences in rebound mammography, and attributed that in part to the digital divide that COVID – 19 had magnified. Specifically, not all technological advances are equally accessible to minority communities – therefore – utilizing community sensitive strategies to spread the word about importance of screening should be considered (for example, telephone engagement).

Covid-19



COVID-19

International Journal of Environmental Research and Public Health

MDPI

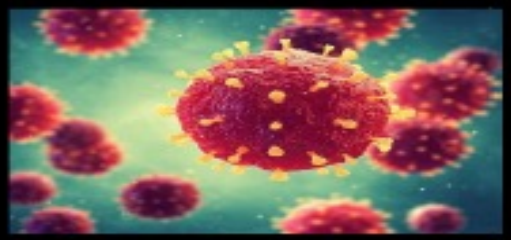
Study Protocol

The Impact of the COVID-19 Pandemic on Cancer Care and Health-Related Quality of Life of Non-Hispanic Black/African American, Hispanic/Latina and Non-Hispanic White Women Diagnosed with Breast Cancer in the U.S.: A Mixed-Methods Study Protocol

Chiara Acquati [1,2,*], Tzuan A. Chen [3,4], Isabel Martinez Leal [3,4], Shahnjayla K. Connors [4,5], Arooba A. Haq [4], Anastasia Rogova [4], Stephanie Ramirez [6], Lorraine R. Reitzel [3,4] and Lorna H. McNeill [2]

- NCI is also funding more research in order to better understand connections among underrepresented racial and ethnic minority populations, social determinants of health (SDOH), and breast cancer outcomes.
- SDOH encompasses 5 domains – economic stability, education access and quality, health care access and quality, neighborhood environment, and social and community context.
- The goal of this mixed-methods research is to examine how SDOH contribute to continuity of care and health-related quality of life among a diverse sample of women, and use the information to inform change in models of care delivery.

Lack of screening



COVID-19

JNCI J Natl Cancer Inst (2021) 113(11): djab097

OXFORD

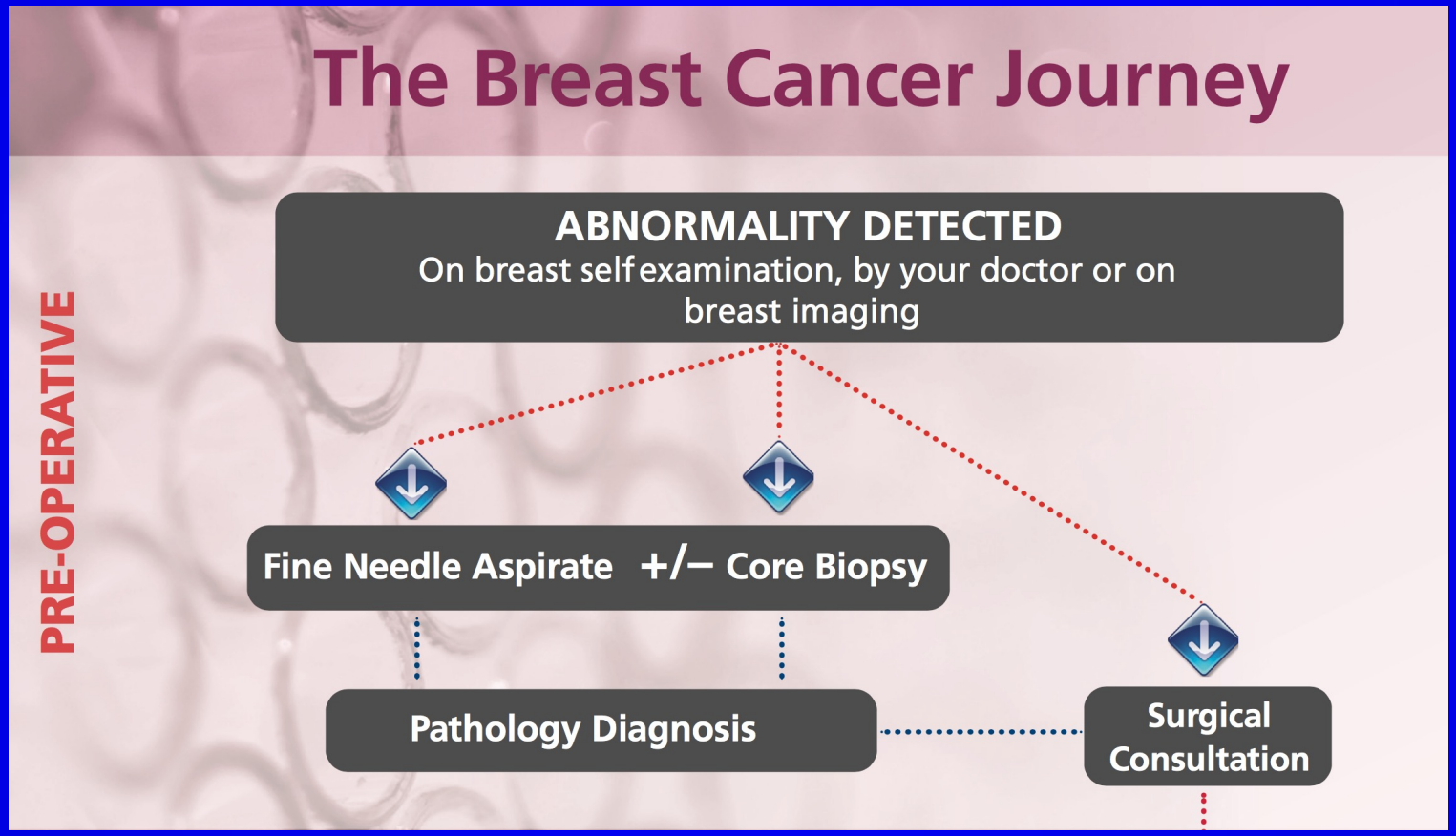
Impact of the COVID-19 Pandemic on Breast Cancer Mortality in the US: Estimates From Collaborative Simulation Modeling

Oguzhan Alagoz,[1,*] Kathryn P. Lowry,[2] Allison W. Kurian,[3] Jeanne S. Mandelblatt,[4] Mehmet A. Ergun,[5] Hui Huang,[6] Sandra J. Lee,[7] Clyde B. Schechter,[8] Anna N. A. Tosteson,[9] Diana L. Miglioretti,[10] Amy Trentham-Dietz,[11] Sarah J. Nyante,[12] Karla Kerlikowske,[13] Brian L. Sprague,[14,*] Natasha K. Stout,[15,*] from the CISNET Breast Working Group

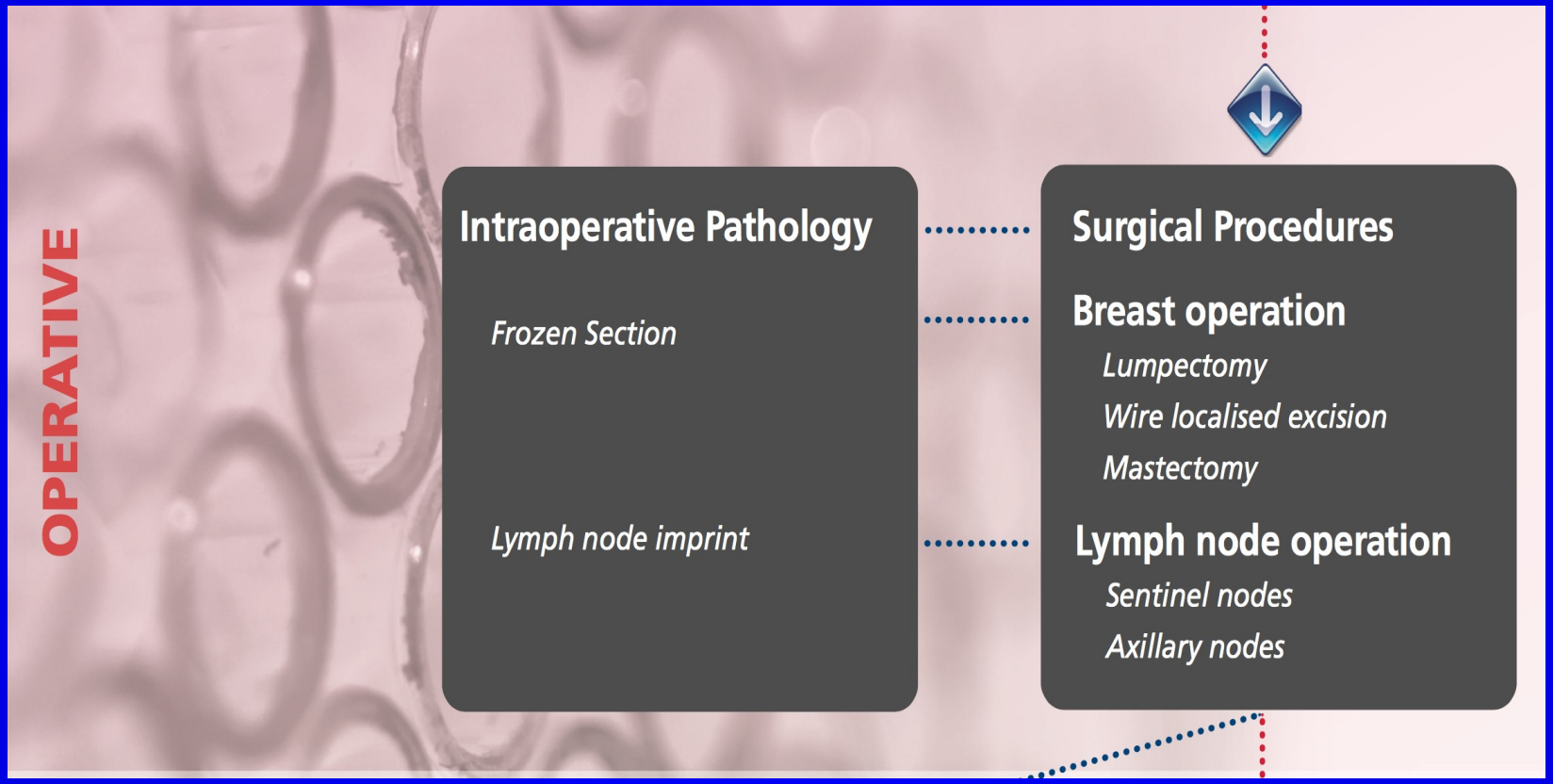
- This NCI funded study, published in JNCI used simulation modeling to estimate that by 2030, nearly 2500 additional breast cancer deaths will have been caused by pandemic related disruptions in screening and care.
- Most importantly, continued efforts to ensure prompt return to screening, and minimizing delays in evaluation of symptomatic women can greatly alleviate the impact of the initial pandemic associated disruptions.

Patient journey

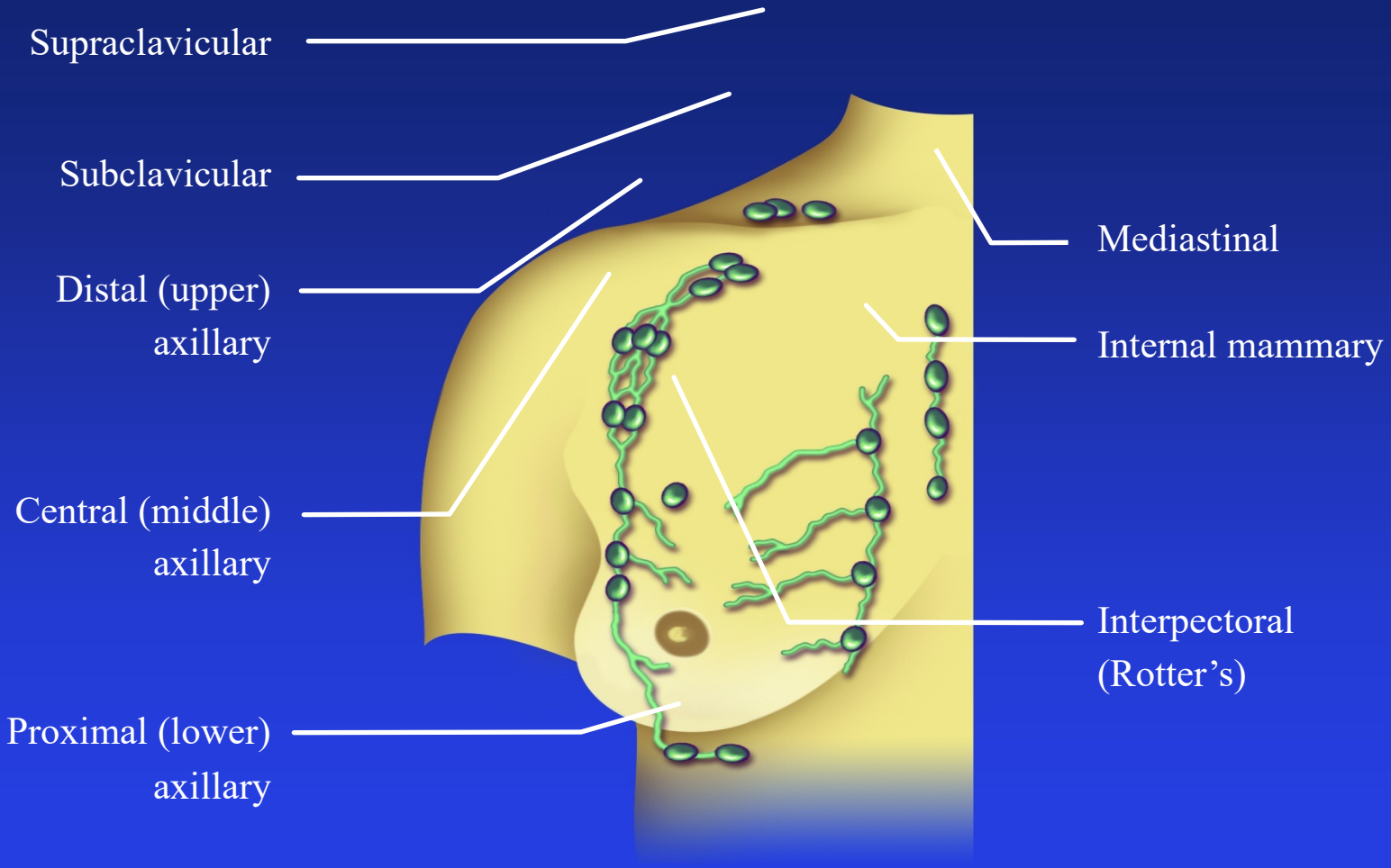
Pre-operative



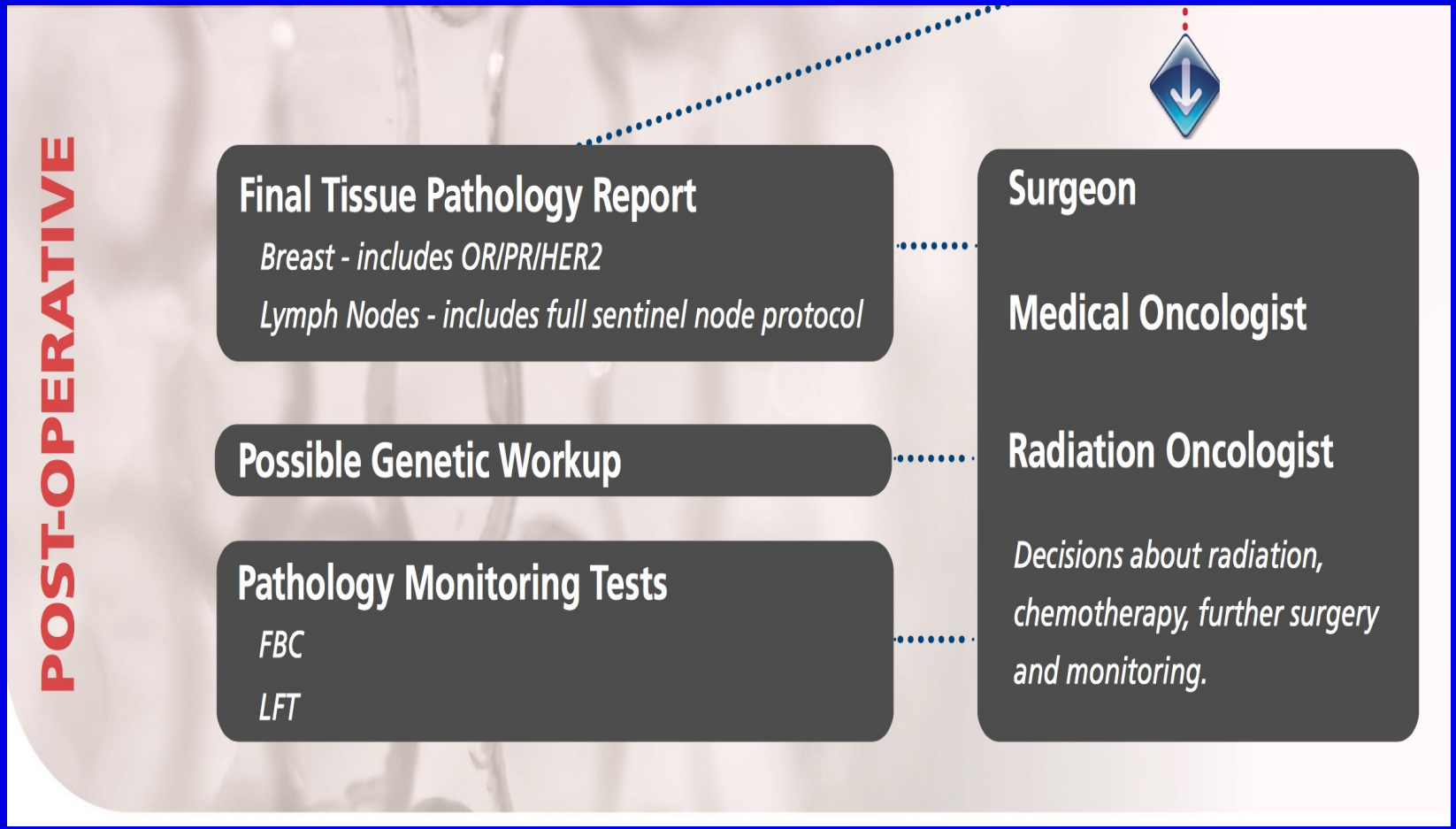
Operative


OPERATIVE
Intraoperative Pathology
Frozen Section
Lymph node imprint
Surgical Procedures
Breast operation
Lumpectomy
Wire localised excision
Mastectomy
Lymph node operation
Sentinel nodes
Axillary nodes

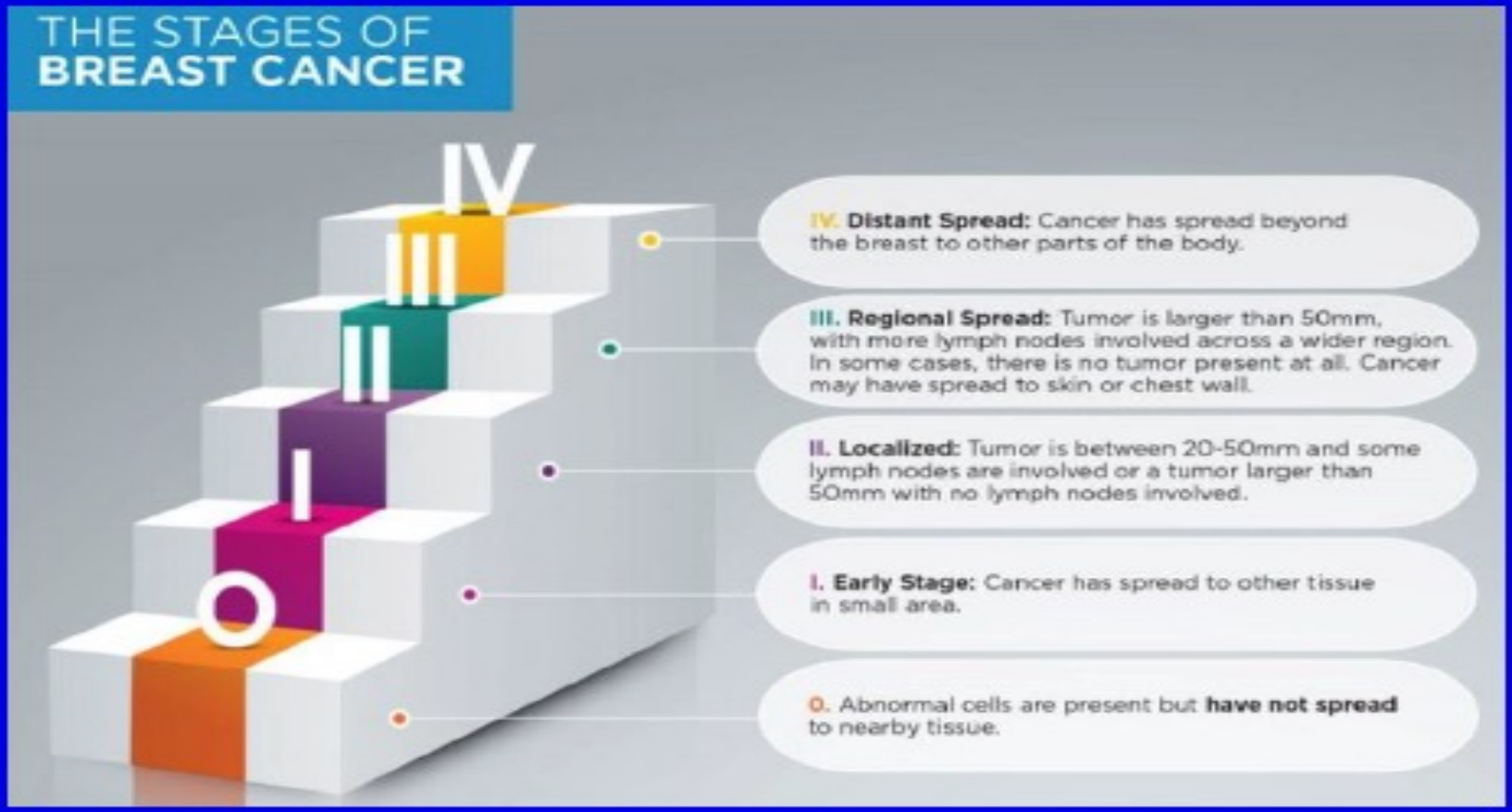
Structure of the Breast : Lymph Nodes



Post-operative



Breast cancer stages



Inflammatory Breast Cancer

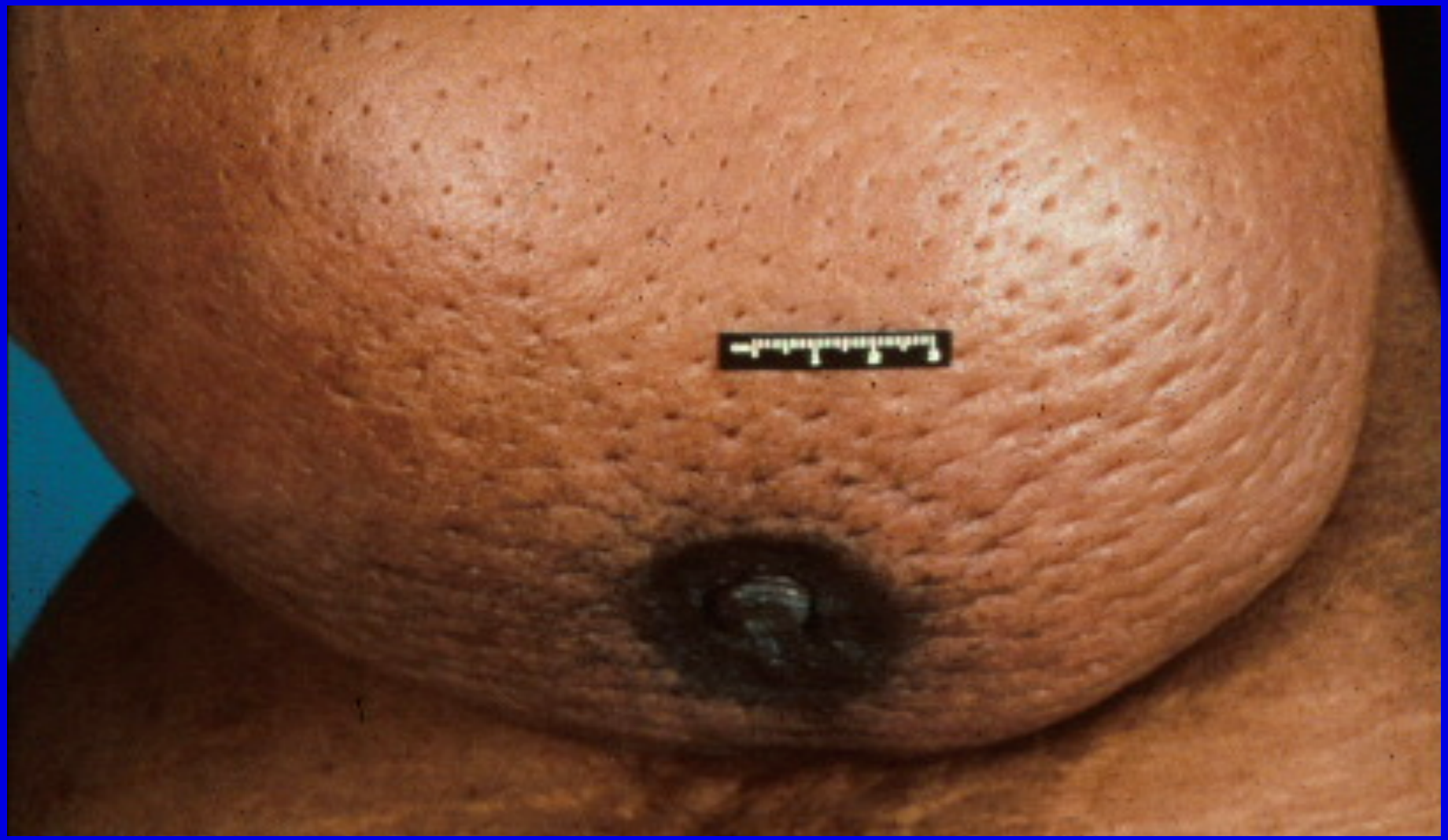
Definition

- A rare form of breast cancer
- Incidence in US ~ 1-5%
- Difficult to track because of variation in diagnostic criteria.
- Malignant cells infiltrate and clog the dermal lymphatics; However, this is NOT a diagnostic criteria for IBC
- The diagnosis is mainly clinical along with confirmed invasive cancer.

Clinical Presentation

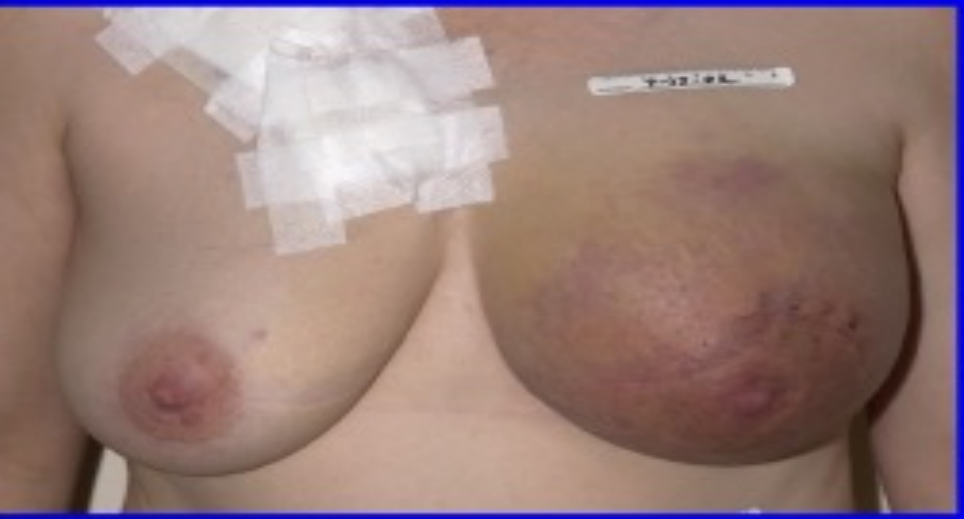
- Confirmed biopsy of invasive breast cancer .
- Rapid onset 3-6 months
- Erythema over ≥ 1/3 of the breast
- Edema (peau d'orange)
- Breast enlargement, often w/o a mass.

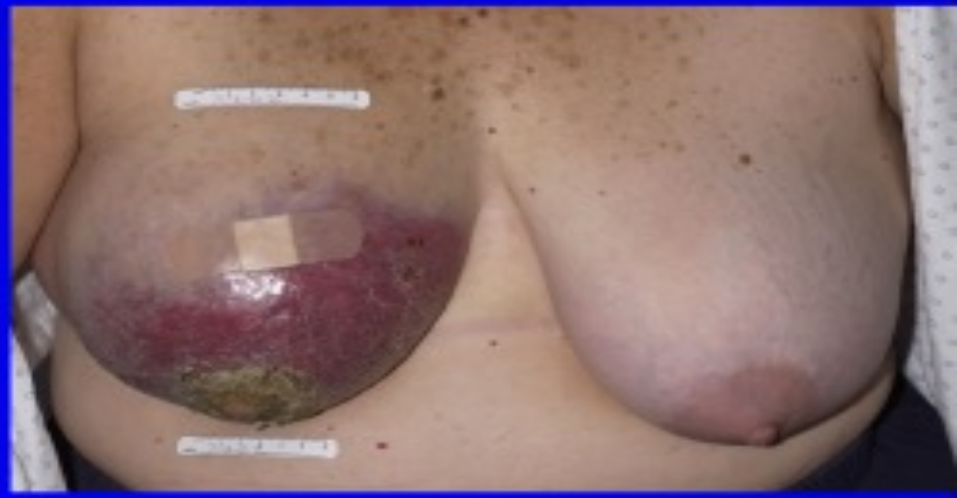
IBC

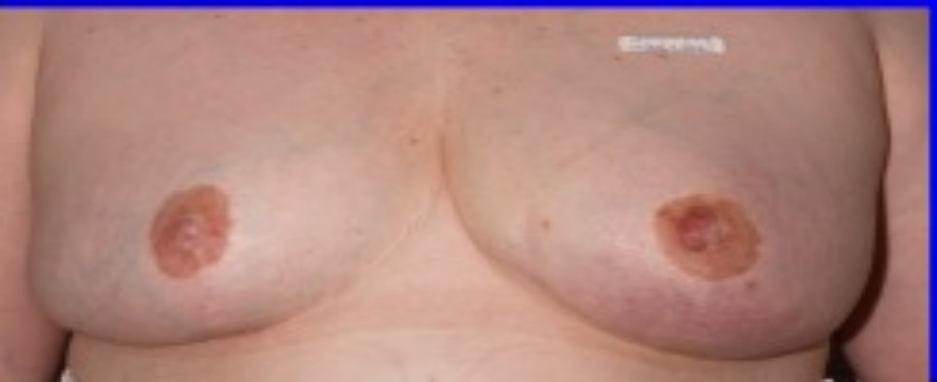


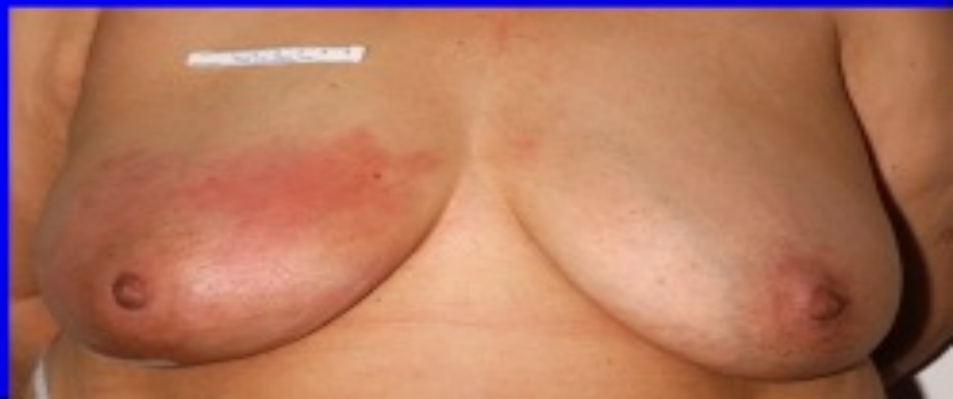
IBC

Clinical Presentations of IBC









Prognostic and Predictive Factors influencing Treatment Decisions

Treatment

- Breast Cancer is commonly treated with various combinations of:
  - surgery
  - radiation therapy
  - chemotherapy
  - hormone therapy
  - targeted therapies

Molecular Profiling

Prognosis and Selection of Therapy Influenced By:

- Menopausal status
- Stage of disease
- Grade of the tumor
- ER/PR status
- HER2/neu amplification
- Histologic type
  favorable histologies:
  - mucinous
  - medullary
  - tubular
- Patient's age and general health
- Presence of known mutations

Molecular diagnostics

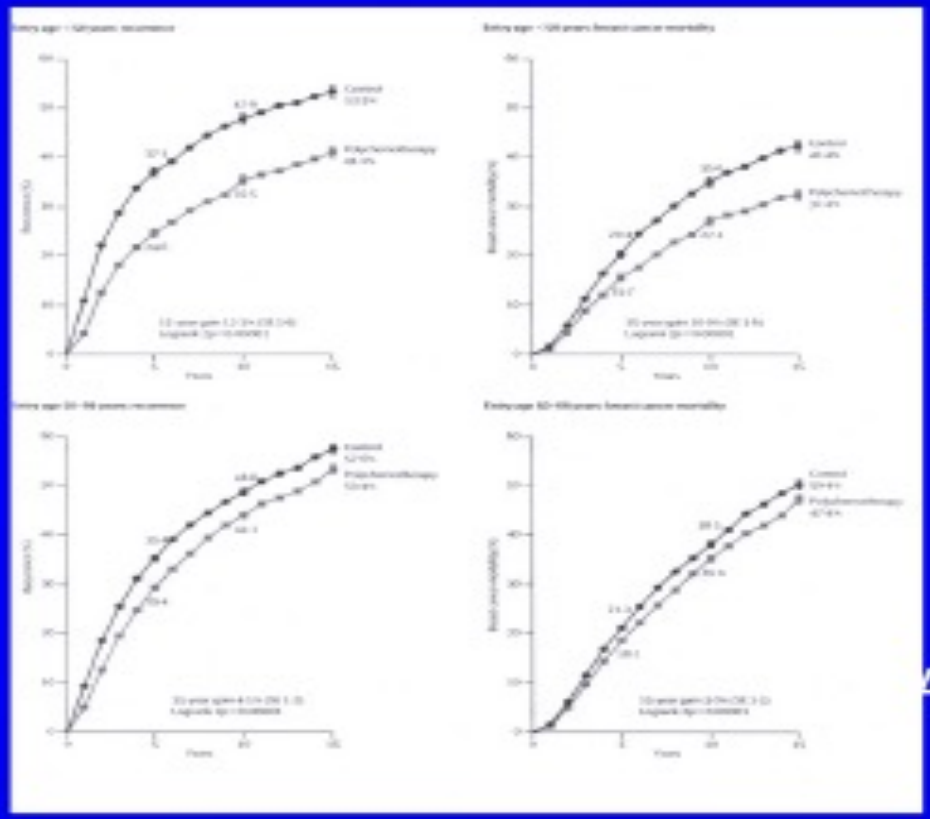
What are the Clinical Implications of Molecular Diagnostics in Breast Cancer?

- Treatment is becoming more personalized for patients, with tumor genomic profiling that could lead to optimal treatment.
- Clinical Next Generation Sequencing (NGS or Tumor Profiling) is increasingly being used to identify potentially actionable mutations in tumor tissue.
- What we don't yet know is if assigning treatment based on specific gene mutations can provide clinical benefit (increasing overall survival) to patients with metastatic tumors.
- Most tumors have multiple mutations and it is often not clear which one to target to achieve maximal benefit. This is an avenue of ongoing investigation

Risk reductions

Absolute Risk Reductions of Relapse and Mortality with Polychemotherapy

Though both age groups do benefit from polychemo the greatest reduction in recurrence and mortality is in those <50.



Age<50

Age 50-69

Recurrence

Mortality

EBCTCG, Lancet 2005

Aromatase inhibitors

Some examples of the many chemotherapies that may be used to treat invasive ductal carcinoma ….

Chemical Name	Trade Name
Doxorubicin (DNA Intercalator)	Adriamycin
Epirubicin (DNA Intercalator)	Ellence
Cyclophosphamide (DNA Alkylator)	Cytoxan
Docetaxel (Microtubule Inhibitor)	Taxotere
Paclitaxel (Mitotic Inhibitor)	Taxol
Capecitabine (Anti-metabolite)	Xeloda
Ixabepilone (Microtubule Inhibitor)	Ixempra
Methotrexate (Folic Acid Antagonist)	Methotrexate
Carboplatin (Cytotoxic)	Paraplatin
5-Flourouracil (5-FU) (anti-Metabolite)	Flourouracil

Example of the many hormonal therapies approved for early stage and locally advanced breast cancer:

Drug	Brand Name	Menopausal Status	IM Pill	Class or Mechanism
Tamoxifen	Nolvadex	Pre & Post	Pill	SERM: antagonist (breast) partial agonist (endometrium)
Anastrozole Letrozole	Arimidex Femara	Post	Pill Pill	Aromatase Inhibitor (AI) Blocks Aromatase, enzyme that converts other hormones to estrogen
Exemestane	Aromasin	Post	Pill	AI
Fulvestrant	Faslodex	Post	IM	Pure Anti-estrogen
Goserelin	Zoladex	Pre	IM	Ovarian Suppression
Leuprolide	Lupron	Pre	IM	Ovarian Suppression

EBCTCG: Benefit of Tamoxifen as Adjuvant *Treatment*

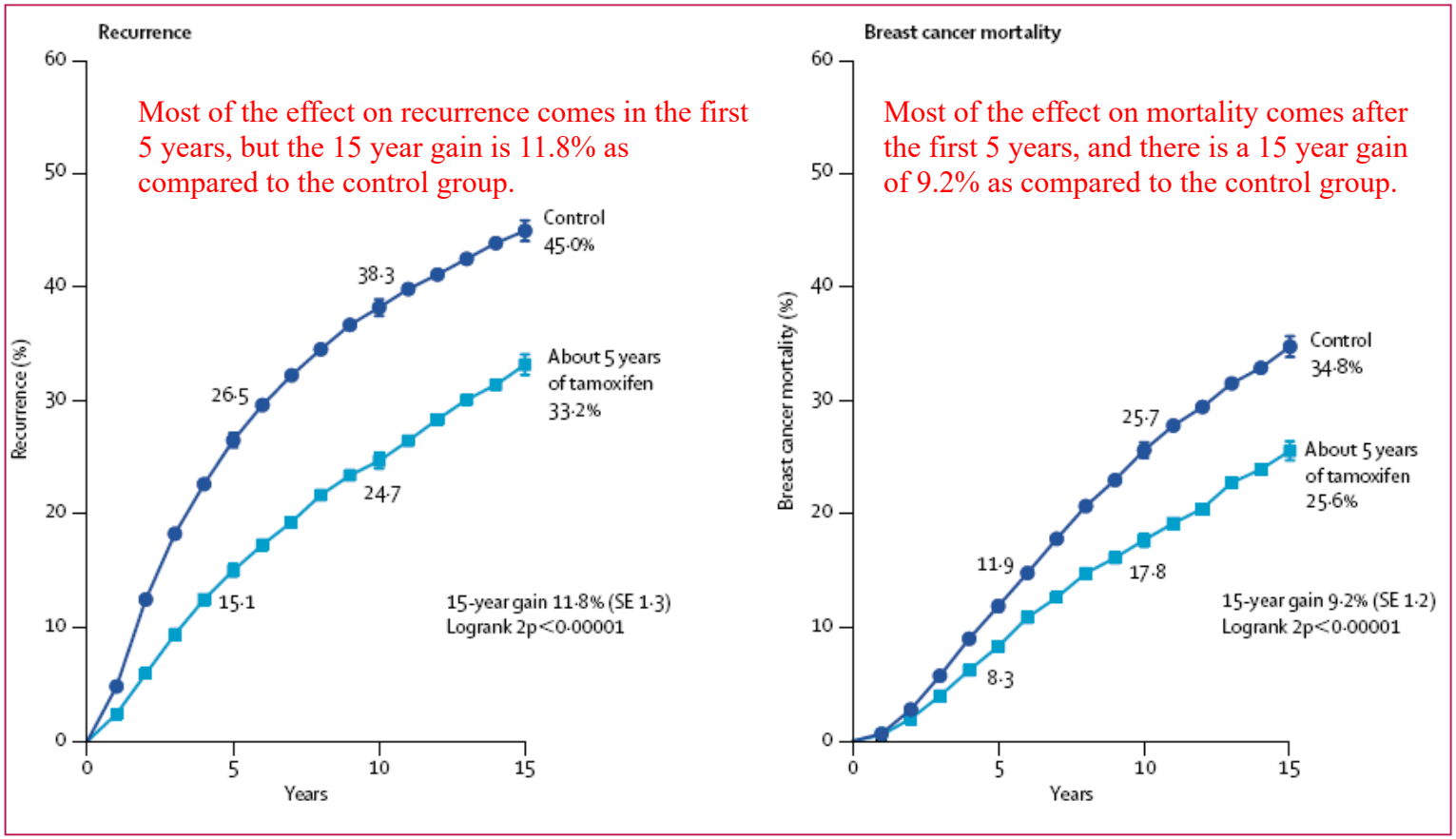


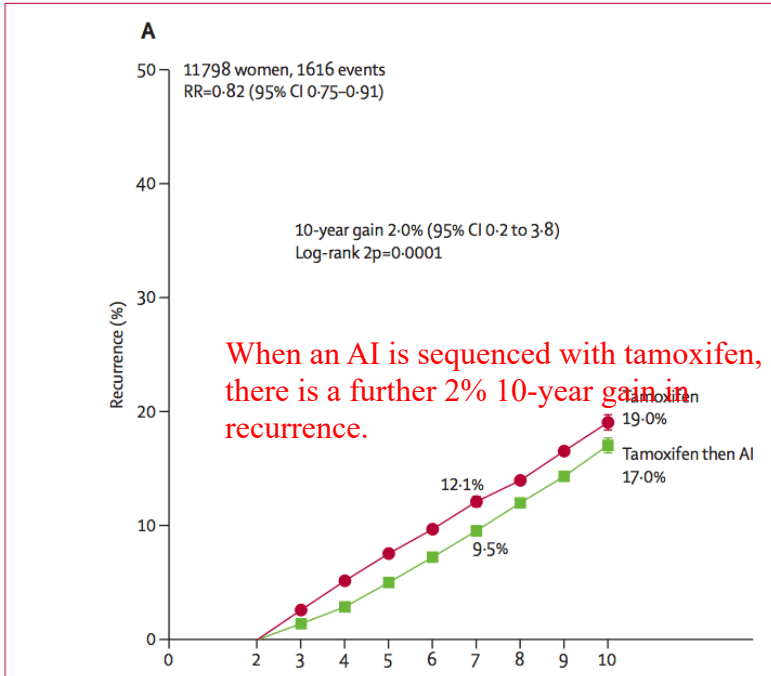
Figure 8: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality**
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

EBCTCG

Lancet, 2014

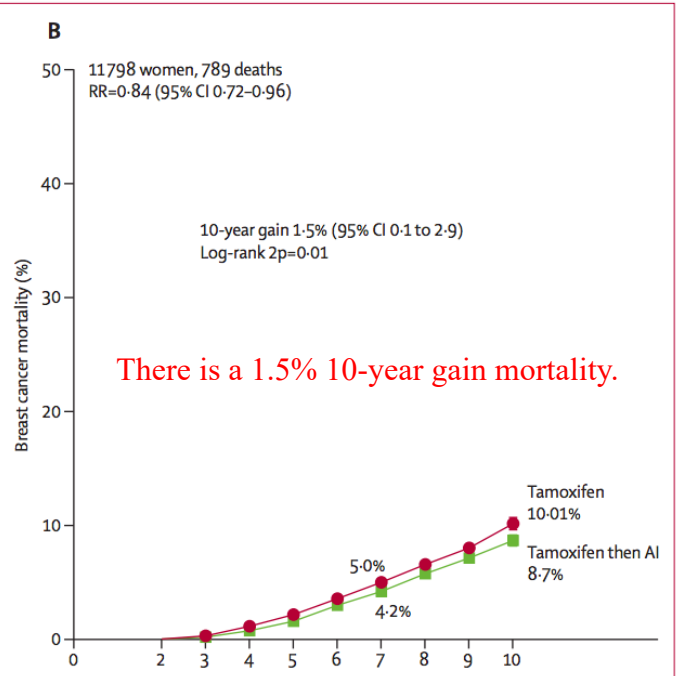
Tamoxifen followed by AI in Adjuvant Setting

Benefit of Sequencing Hormonal Therapies



Recurrence rate/year (%), events/woman-years and log-rank statistics

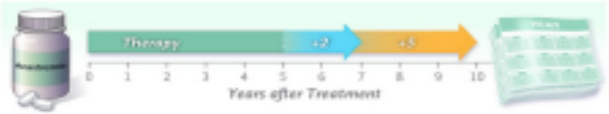
Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8

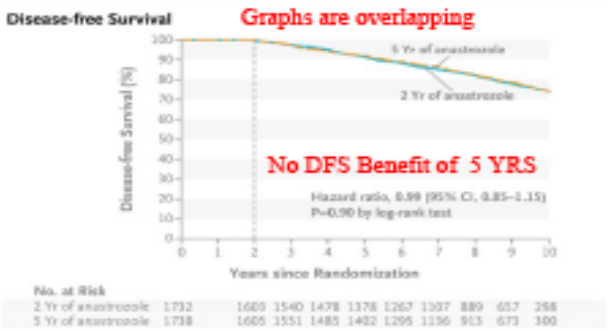


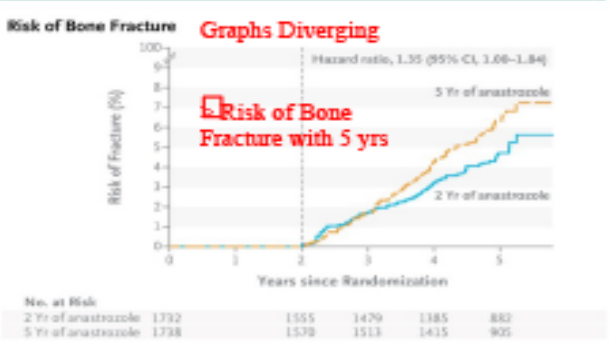
Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·37 (0·25–0·48)	1·28 (1·12–1·44)	1·68 (1·63–1·72)
Tamoxifen	0·56 (0·43–0·70)	1·40 (1·26–1·56)	2·54 (2·45–2·59)
Rate ratio (95% CI)	0·65 (0·44–0·96)	0·91 (0·77–1·08)	0·69 (0·48–1·00)
from (O-E)/V	−11·0/25·8	−11·9/132·0	−10·6/28·9

Aromatase inhibitor

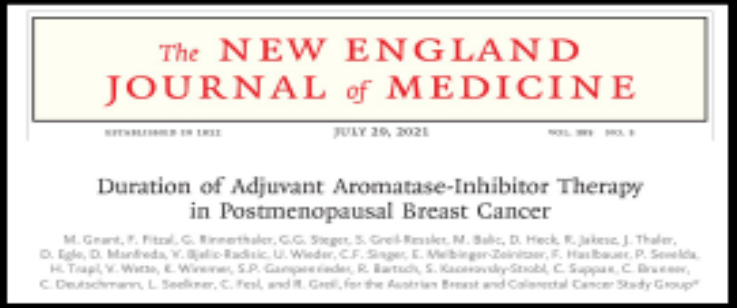






CONCLUSIONS

Postmenopausal women with hormone-receptor–positive breast cancer at average risk do not benefit from extending adjuvant aromatase-inhibitor therapy beyond a total of 7 years.



- In this prospective phase 3 trial, post-menopausal women with HR+ breast cancer, who had already received 5 years of adjuvant endocrine therapy were randomized to receive an additional 2 years (7 total) or an additional 5 years (10 total)
- The primary end-point was DFS

CONCLUSION:

- Extending HR therapy by 5 years provided no benefit over a 2 year extension, but was associated with a greater risk of bone fracture.

Examples of Targeted Therapies

Chemical Name	Trade Name	Mechanism	Indication
Trastuzumab	Herceptin	Humanized MoAb that binds selectively to the HER2 protein, and suppresses activity that would lead to cell proliferation	Adjuvant therapy along with chemo in HER2+ breast cancer; Neoadjuvant therapy in large HER2+, also used in metastatic HER2+ breast cancers
Pertuzumab	Perjeta	Humanized MoAb that binds to the extracellular domain II of HER2. it inhibits ligand dependent HER2 – HER3 Dimerization, reduced signalling through PI3K/AKT	Indicated for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2+ locally advanced inflammatory or early stage breast cancer.
Ado-trastuzumab Emantasine	Kadcyla	Herceptin + Emantasine. Delivers Emantasine to cancer cells in a targeted way.	Approved to treat HER2 positive metastatic breast cancer, previously treated with Herceptin and Taxane

Targeted therapies

Examples of Targeted Therapies (HER2+ Disease): Ab-Drug Conjugates

Chemical Name	Trade Name	Mechanism	Indication
Ado-trastuzumab Emantasine (T-DM1)	KADCYLA	Trastuzumab (MoAb) + Emantasine (cytotoxic agent) Delivers Emantasine to cancer cells in a targeted way.	Approved (Feb. 2013) to treat HER2 positive metastatic breast cancer, previously treated with Herceptin and Taxane
Fam-Trastuzumab Deruxtecan-Nxki (T-DXd)	Enhertu	Trastuzumab (MoAb) + deruxtecan-nxki (topoisomerase inhibitor)	Approved (Dec. 2019) to treat: • Unresectable HER-2 positive breast cancer. • Metastatic HER-2 positive breast cancer that has been treated with two or more anti-Her2 therapies

Targeted therapies

Examples of Targeted Therapies (HER2+ Disease) – TKI's

Chemical Name	Trade Name	Mechanism	Indication
Lapatinib	Tykerb	Small Molecule Tyrosine Kinase Inhibitor Human EGFR type 1 and type 2 tyrosine kinase inhibitor. It binds to the intracellular phosphorylation domain to prevent receptor auto-phosphorylation upon ligand binding.	Lapatinib + Xeloda to treat advanced stage HER2+ breast cancer that has stopped responding to anthracyclines, taxanes, and Herceptin. Lapatinib + Letrozole for the treatment of postmenopausal HR+ HER2+ metastatic breast cancer
Neratinib	Nerlynx	Small Molecule Tyrosine Kinase Inhibitor	• Approved to treat Her2-positive breast cancer: (by FDA July 2017) ✓ As a single agent for the treatment of early stage disease after trastuzumab (Herceptin) based therapy ✓ In combination with capecitabine (Xeloda) as a 3rd line HER2 agent to treat advanced or metastatic disease
Tucatanib	Tukysa	Small Molecule Tyrosine Kinase Inhibitor	Approved by FDA April 2020 ✓ In combination with Trastuzumab (Herceptin) and Capecitabine (Xeloda) in unresectable or metastatic disease, including when cancer has spread to the brain. ✓ Given when other treatments have failed.

Targeted therapies

More Targeted Therapies ...

Chemical Name	Trade Name	Mechanism	Indication
Alpelisib	Piqray	Inhibits PIK3 in the PI3K/AKT signaling pathway, ultimately inhibiting pathway activation. This results in inhibition of cell growth and survival. ** PIK3CA missense mutations occur in about 40% of ER+ breast cancers	Approved in combination with fulvestrant for post-menopausal women with HR+, HER2 negative, PIK3CA-mutated, advanced or metastatic breast cancer. **Approved May 24, 2019, based on the phase 3 Solar-1 study**
Everolimus	Affinitor	mTOR inhibitor Interacts with MTORC1 and inhibits downstream signaling.	Postmenopausal advanced HR+ HER2- breast cancer in combination with exemestane after progression on letrozole and anastrozole. **Approved April 10, 2018**

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Olaparib	Lynparza	PARP inhibitor Inhibits enzyme involved in DNA Repair Since BRCA mutated cells are incapable of homologous repair of DS DNA breaks, additional PARP inhibition causes genomic instability and cell death.	1st targeted therapy approved for gBRCAm breast ca (HER2 – and metastatic ***Approved Jan. 2018***
Talazoparib	Talzenna	PARP inhibitor Inhibits enzyme involved in DNA Repair	germline-BRCAm, HER2 – locally advanced or metastatic breast cancer. *(Based on germline testing by Myriad Genetic Laboratories)* ***Approved Oct. 2018***

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Palbociclib	Ibrance	CDK4/6 Inhibitor Aberrations in the CDK-RB pathway are common in breast cancer. Consequently, inhibition of this pathway is an attractive therapeutic strategy. Inactivation of CDK4/6-cyclin D1complexes helps control cell growth by inducing G1 arrest and reducing cell cycle progression.	HR+ HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor Or With fulvestrant in women with disease progression following endocrine therapy.
Ribociclib	Kisqali	CDK4/6 inhibitor	Ribociclib + AI for initial endocrine therapy in postmenopausal HR+ HER2- advanced/metastatic breast cancer. Ribociclib + Fulvestrant in HR+ HER2- advanced/metastatic breast cancer as initial Rx, or following progression on endocrine Rx
Abemaciclib	Verzenio	CDK4/6 inhibitor	HR+ HER2 – advanced metastatic BrCa in combination with an AI or fulvestrant.

ENHURTU

- FDA approved Enhertu (fam-trastuzumab-deruxtecan-nxki) for the treatment of patients with unresectable or metastatic HER2-low breast cancer subtype, which is a newly defined subset of HER2-negative breast cancer.
- Approximately 85% of new cases of breast cancer were previously considered to be HER2-negative. Of that proportion, about 60% of patients previously classified as HER2-negative subtype, can now be considered HER2-low.
- Prior to this approval, HER2-low patients received only endocrine therapy or chemotherapy.
- HER2-low is a new classification of the HER2 subtype that describes breast cancer that has some HER2 protein on the cell surface, but not enough to be classified as HER2-positive.

FDA NEWS RELEASE

FDA Approves First Targeted Therapy for HER2-Low Breast Cancer

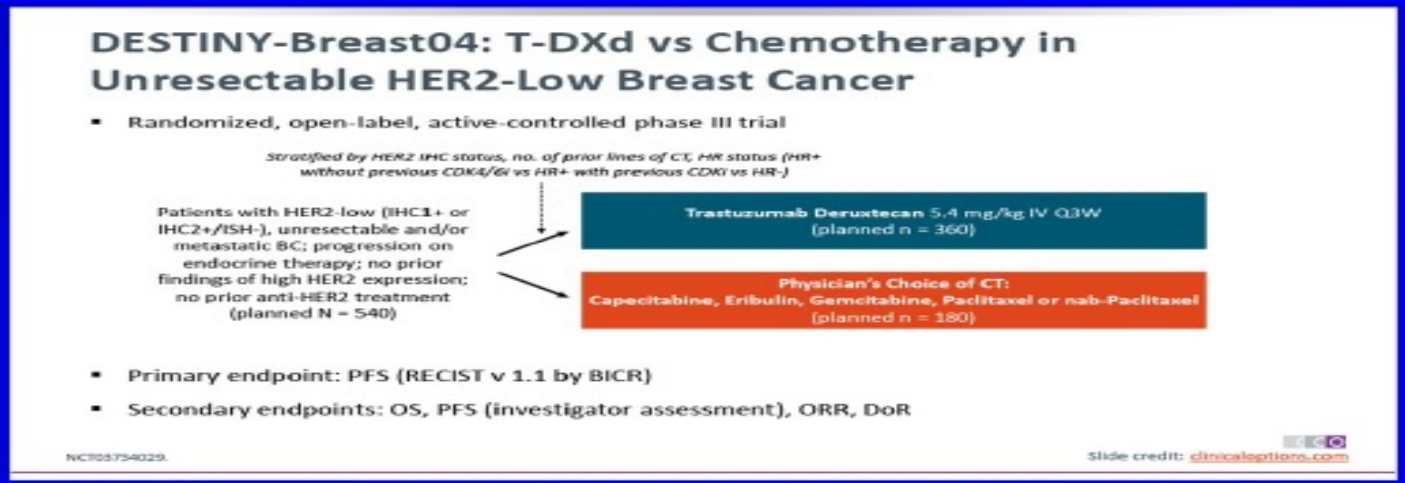
News-Maker 2022!!

IHC 1+

OR

IHC2+/ FISH -

DESTINY trial



IHC 1+

OR

IHC2+/ FISH -

- Trastuzumab deruxtecan improved median PFS by 4.8 months and median OS by 6.6 months compared with standard single agent chemotherapy in this heavily pre-treated patient population.
- These data established a new standard of care for patients with HER2-low metastatic breast cancer.
- In addition to providing a new treatment option for patients with HER2-low disease, these findings also justify the shift in the way pathology laboratories report HER2 results,

Targeted therapies

Examples of Targeted Therapies (HER2+ Disease): Ab-Drug Conjugates

Chemical Name	Trade Name	Mechanism	Indication
Ado-trastuzumab Emantasine (T-DM1)	KADCYLA	Trastuzumab (MoAb) + Emantasine (cytotoxic agent) Delivers Emantasine to cancer cells in a targeted way.	**Approved (Feb. 2013)** to treat HER2 positive metastatic breast cancer, previously treated with Herceptin and Taxane **Approved (May 2019)** as adjuvant therapy in early stage disease if residual tumor remained following neo-adjuvant therapy.
Fam-Trastuzumab Deruxtecan-Nxki (T-DXd)	Enhertu	Trastuzumab (MoAb) + deruxtecan-nxki (topoisomerase inhibitor)	**Approved (Dec. 2019)** to treat: • Unresectable HER-2 positive breast cancer. • Metastatic HER-2 positive breast cancer that has been treated with two or more anti-Her2 therapies • (3rd line)
			• **Approved in 2021** for 2nd line use after Herceptin, following phase III head to head trial with T-DM1 • **Approved 8/22** for HER2-Low Breast Cancer

Pembrolizumab

FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer

On July 26, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

- **Approval based on Keynote-522 - a randomized, multicenter, double-blind, placebo controlled trial conducted in 1174 patients with newly diagnosed, untreated high-risk early stage TNBC.**
- **Patients were enrolled regardless of PDL-1 expression.**
- **Patients were randomized to either pembro + chemo or placebo + chemo**

- **Measures of efficacy: pCR, EFS**
- **The pathological complete response (pCR) was 63% for patients who received pembro + chemo compared with 56% for patients who received placebo + chemo**
- **The number of patients who experienced an EFS "event" was 16% in pembro arm and 24% in placebo arm.**

Treatment

MYTH:

When treatment is over, you're finished with breast cancer.

FACT:

Breast Cancer can have long-term impact on people's lives and well-being.

- Patients often report that their family and friends expect them to move on after their primary treatment is completed.
- In reality, targeted treatments such as herceptin, tamoxifen, and aromatase inhibitors can go on for much longer, surgeries for those pursuing breast reconstruction can occur over several months, and for those with metastatic (stage IV) breast cancer, treatment will last for the rest of their lives.

Summary

- Patients can experience long-term physical side effects such as pain and tightness from surgeries, fatigue, neuropathy from previous chemotherapy, menopausal symptoms from either on-going endocrine therapies or the occurrence of early menopause due to certain chemotherapies, as well as other symptoms depending on treatment regimens.
- Also, **Not To Be Forgotten** are the long-term social and emotional effects the journey has taken on the patient.
- There is long-lasting anxiety, fear of recurrence, and relationship changes – among many, many impactful issues.
- As Physicians, we need to embrace the Biopsychosocial Perspective on Medicine, and learn to treat the whole patient, and not just the disease.
- As medical professionals, it is also our responsibility to help educate family and caregivers as to the needs of the patient, beyond the immediate care.
- We need to keep in mind that each patient's journey is unique, and we need to connect with our patients beyond simply prescribing chemotherapy.

Thank you