Farah Zia

Farah Zia, M.D.

Medical Officer/Physician
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Dr. Farah Zia is a and Medical Oncologist, with a sub-specialization in Breast and Gynecologic Cancers. She received her Doctor of Medicine degree from The George Washington University School of Medicine & Health Sciences, and completed her internship and residency training at The George Washington University Hospital. Dr. Zia then pursued further training at The National Institutes of Health, and completed a dual fellowship in Hematology & Oncology as well as a Cancer Therapy Evaluation Program Fellowship, gaining experience in clinical trials and drug development.

Dr. Zia worked as a community physician in Fairfax VA, then returned to the National Cancer Institute (NCI) to pursue her interest in investigative medicine, and joined The Division of Cancer Treatment & Diagnosis (DCTD) as a Medical Officer. She is an active member of the Warren G. Magnuson Clinical Center Medical Staff, and continues patient care through the Center for Cancer research (CCR) Women's Malignancies Branch (WMB), where she is an associate investigator on several breast and gynecologic cancer clinical trials.

Dr. Zia is an active participant in the education of NIH students and fellows. She serves as an Attending Physician on the NCI Medical Oncology Service (MOS), and supervises medical students, residents, and fellows in patient care activities and participates in weekly journal club and didactics. Dr. Zia is also a member of the VA Chapter of the American College of Physicians, and serves on the Women's Health Committee. Her career track includes oncology drug development, women's malignancies, women's health, and the development of integrative strategies to improve the quality of life of all patients, including those with cancer.

Dr. Zia has been named a Washingtonian Magazine Top Doctor for 2024, as well as being recognized by Marquis Who's Who in America in the field of Clinical Research.

Breast cancer

Breast Cancer:
Overview
Prevention, Diagnosis, Treatment

Farah Zia, MD
Medical Officer
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Attending Physician & Clinical Research:

Center for Cancer Research
Women's Malignancies Branch

NIH NATIONAL CANCER INSTITUTE

TRACO Lecture
October 23rd 2023

Breast cancer

Breast anatomy

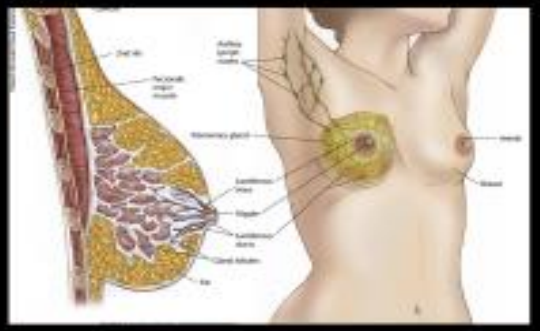
Breast Anatomy

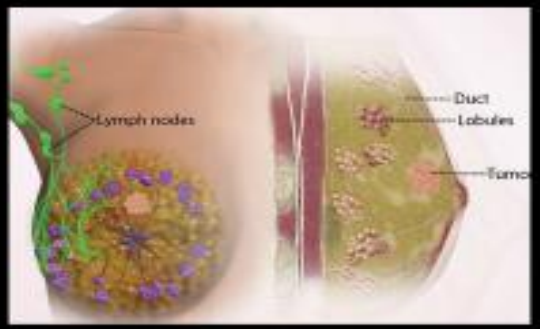
Embedded within fatty and fibrous tissue:

- 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**





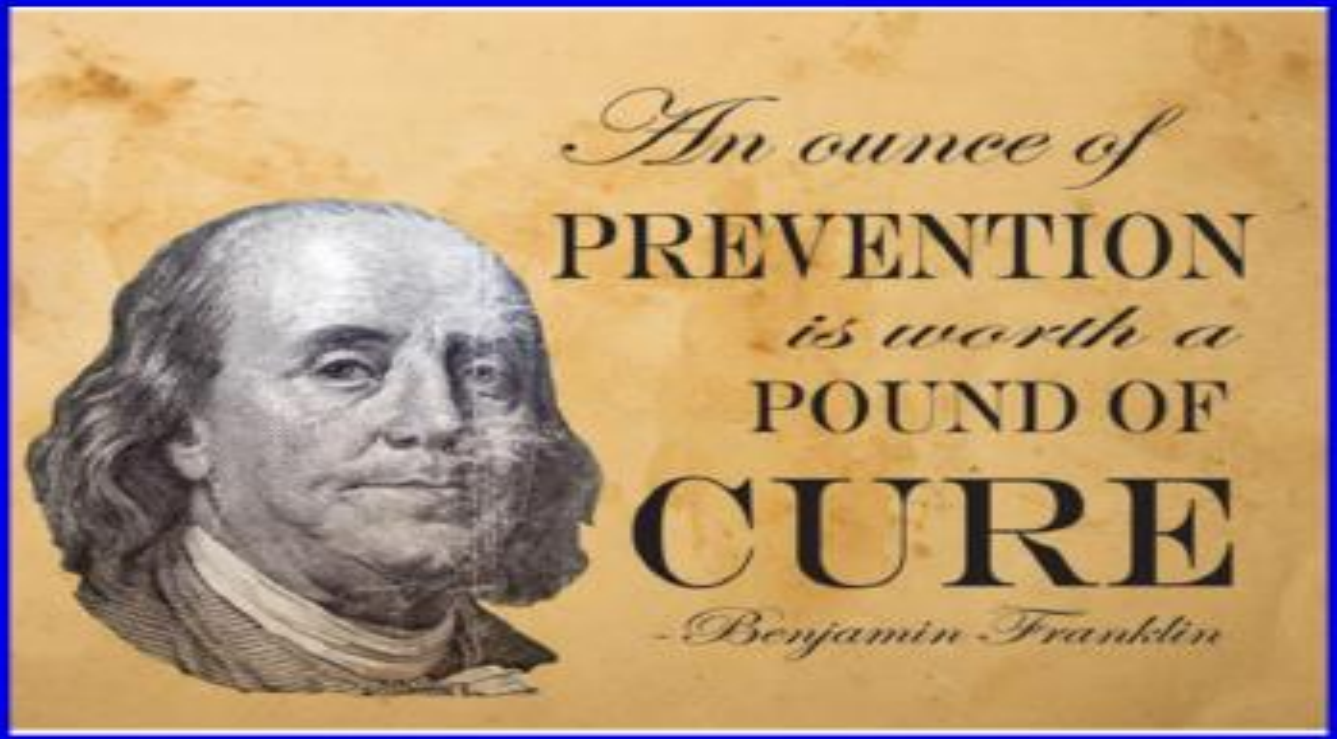
Breast Cancer

- *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

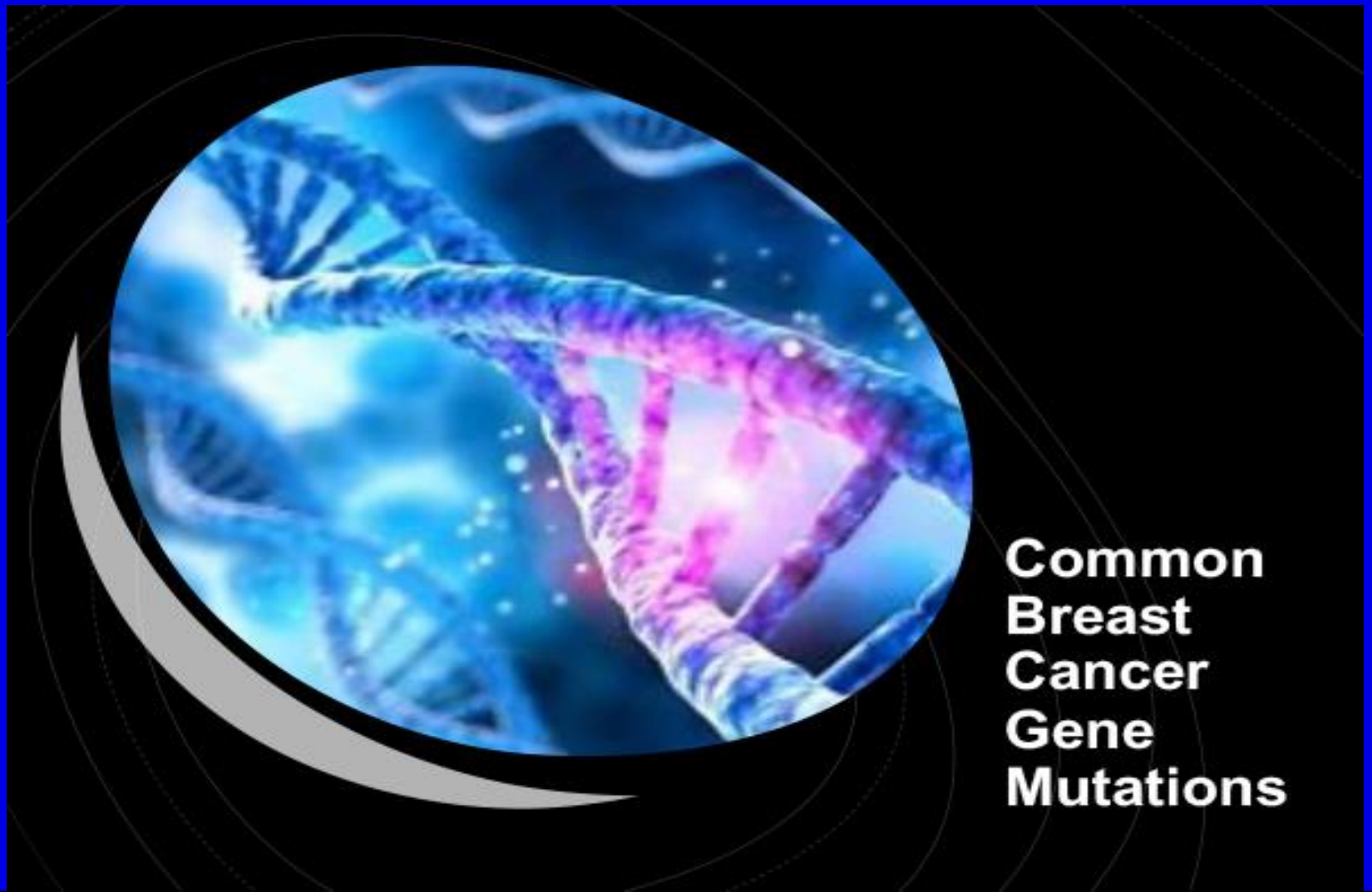
Prevention

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

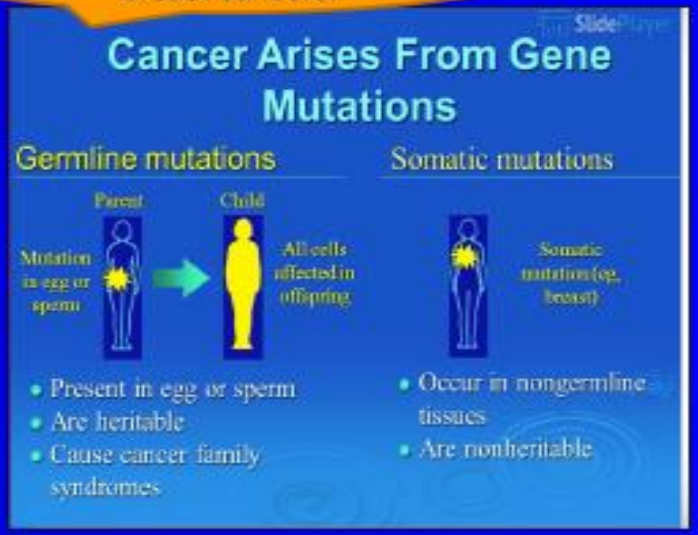
GENES



Mutations

Germline VS Somatic Mutations

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

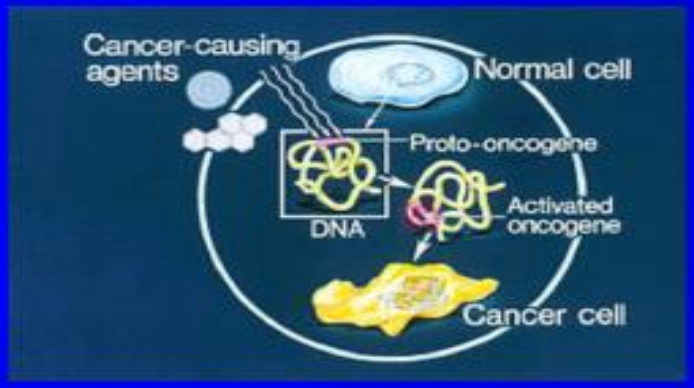


- Many mutations, such as those found in the BRCA1 and BRCA 2 genes, are passed down in an autosomal dominant pattern.
- 1 bad gene from 1 parent = increased risk

- 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.

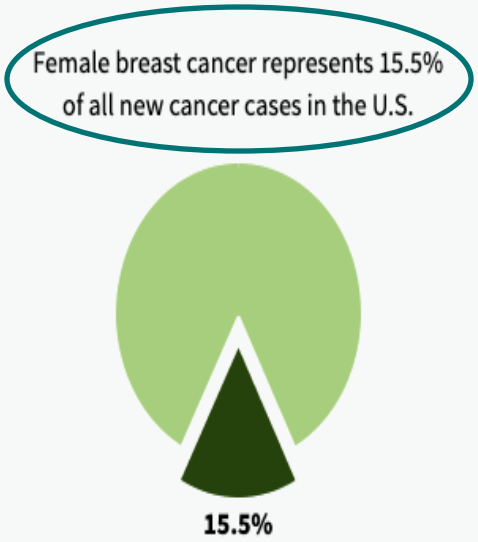
Breast Cancer Statistics

Cancer statistics

How Common Is This Cancer?

Compared to other cancers, female breast cancer is fairly common.

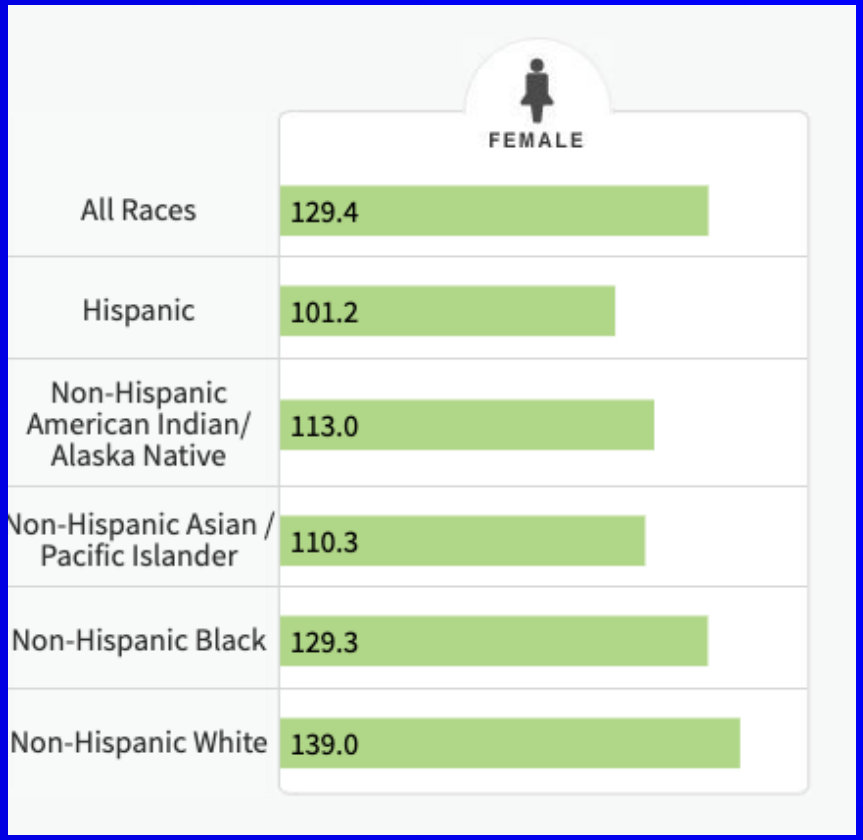
	Common Types of Cancer	Estimated New Cases 2024	Estimated Deaths 2024
1.	Breast Cancer (Female)	310,720	42,250
2.	Prostate Cancer	299,010	35,250
3.	Lung and Bronchus Cancer	234,580	125,070
4.	Colorectal Cancer	152,810	53,010
5.	Melanoma of the Skin	100,640	8,290
6.	Bladder Cancer	83,190	16,840
7.	Kidney and Renal Pelvis Cancer	81,610	14,390
8.	Non-Hodgkin Lymphoma	80,620	20,140
9.	Uterine Cancer	67,880	13,250
10.	Pancreatic Cancer	66,440	51,750



SEER: Surveillance, Epidemiology, and End Results Program, NCI

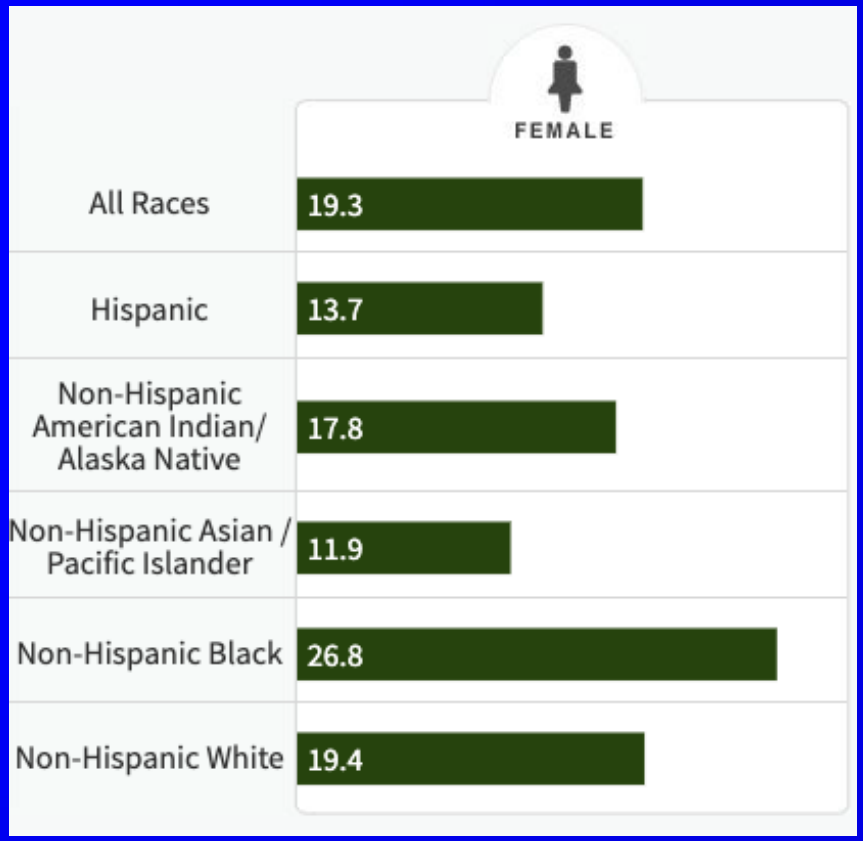
Rates of Incidence and Death By: Race and Ethnicity

Who Gets This Cancer



Rate of New Cases per 100,000 Persons

Who Dies From This Cancer



Death Rate per 100,000 Cases

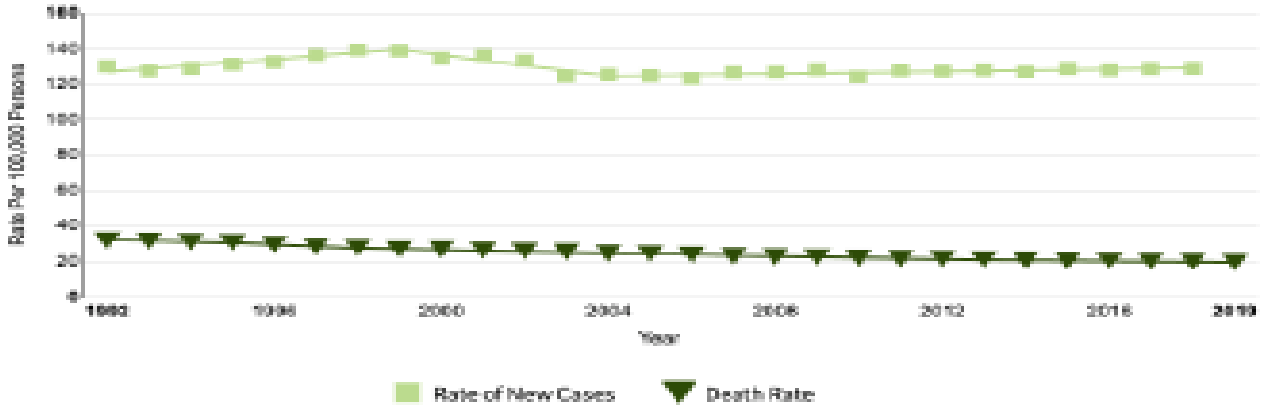
Breast cancer statistics

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.

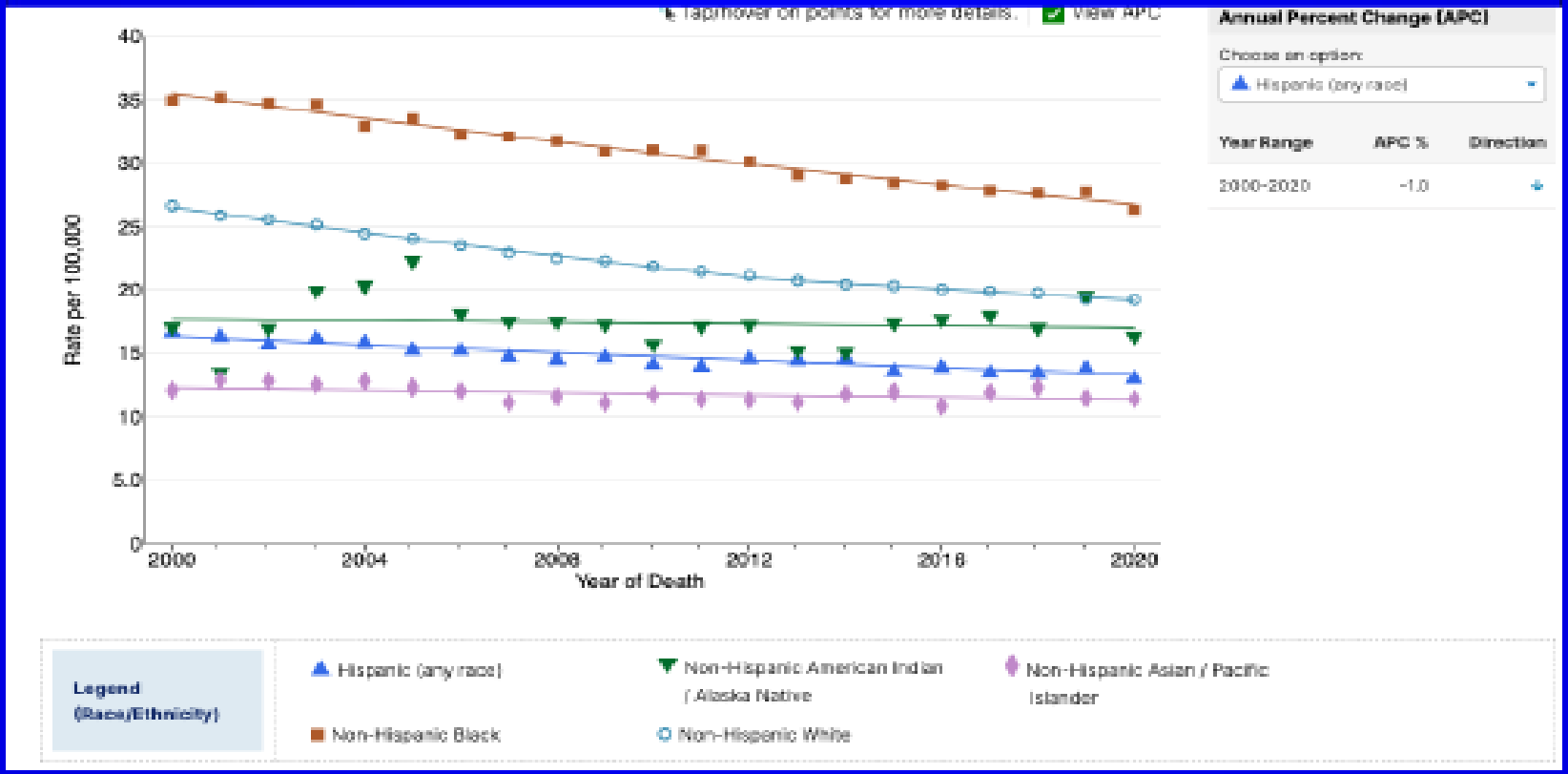
MEN:

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

Age-adjusted mortality

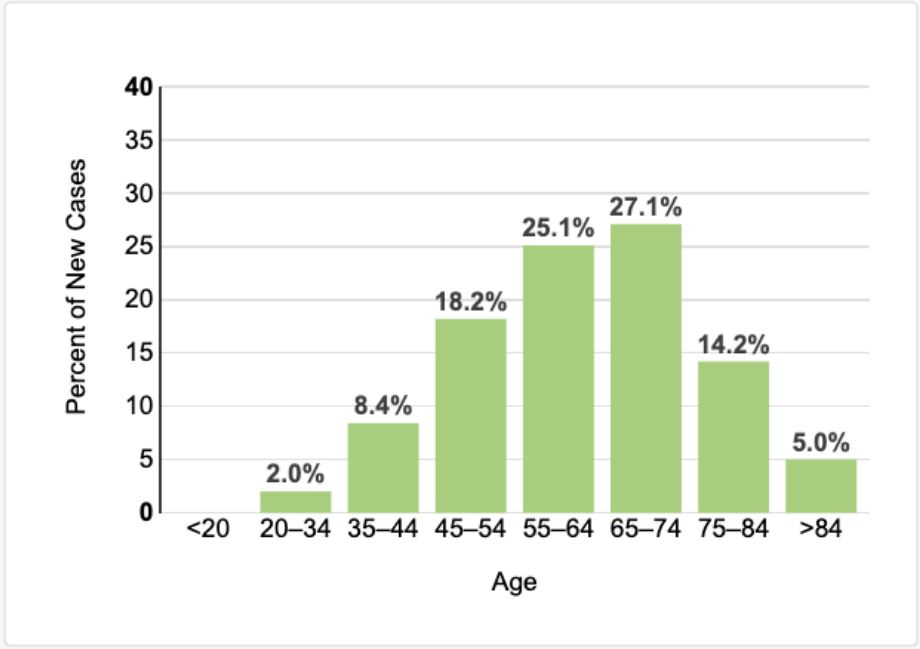
Age –Adjusted U.S. Breast Cancer Mortality Rates

*By Race/Ethnicity, Female, All Ages



Percent of New Cases by Age Group

Percent of New Cases by Age Group: Female Breast Cancer



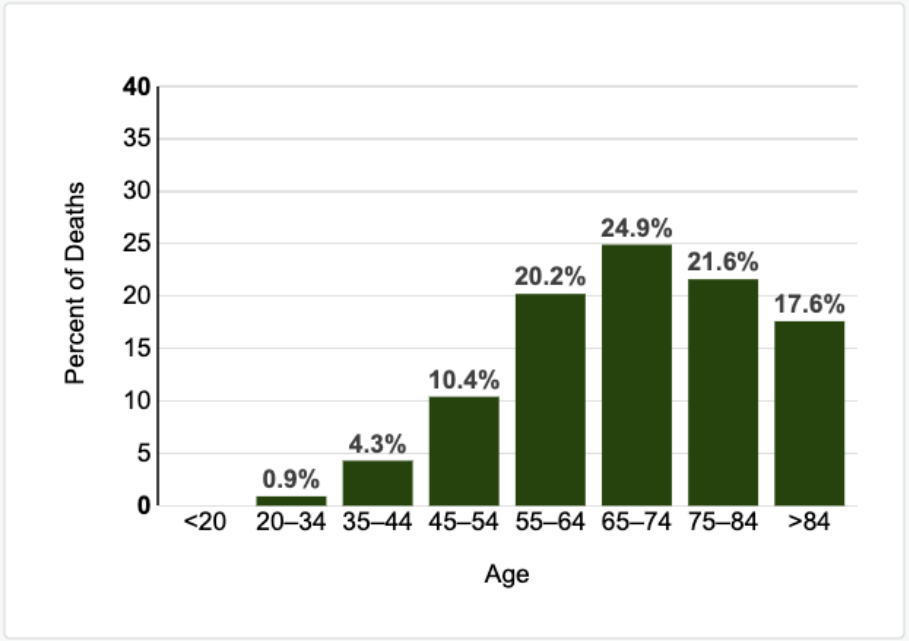
Female breast cancer is most frequently diagnosed among women aged 65–74.

Median Age At Diagnosis
63

SEER 22 2017–2021, All Races, Females

Percent of Deaths by Age Group

Percent of Deaths by Age Group: Female Breast Cancer



The percent of female breast cancer deaths is highest among women aged 65–74.

Median Age At Death
70

U.S. 2018–2022, All Races, Females

Early Detection

Breast lump

Myth:

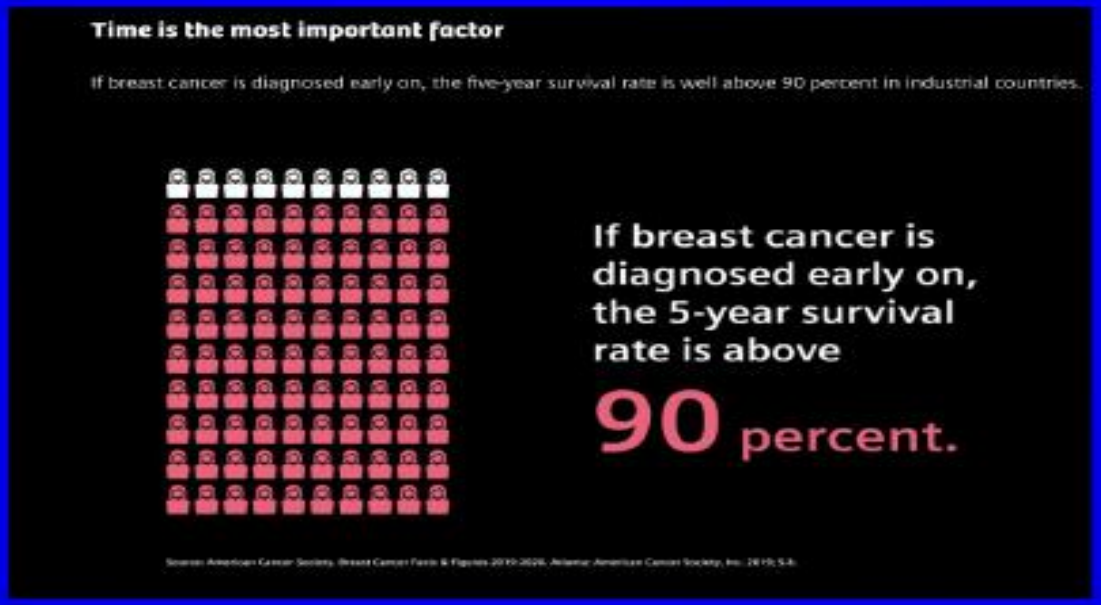
Breast cancer always causes a lump you can feel

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

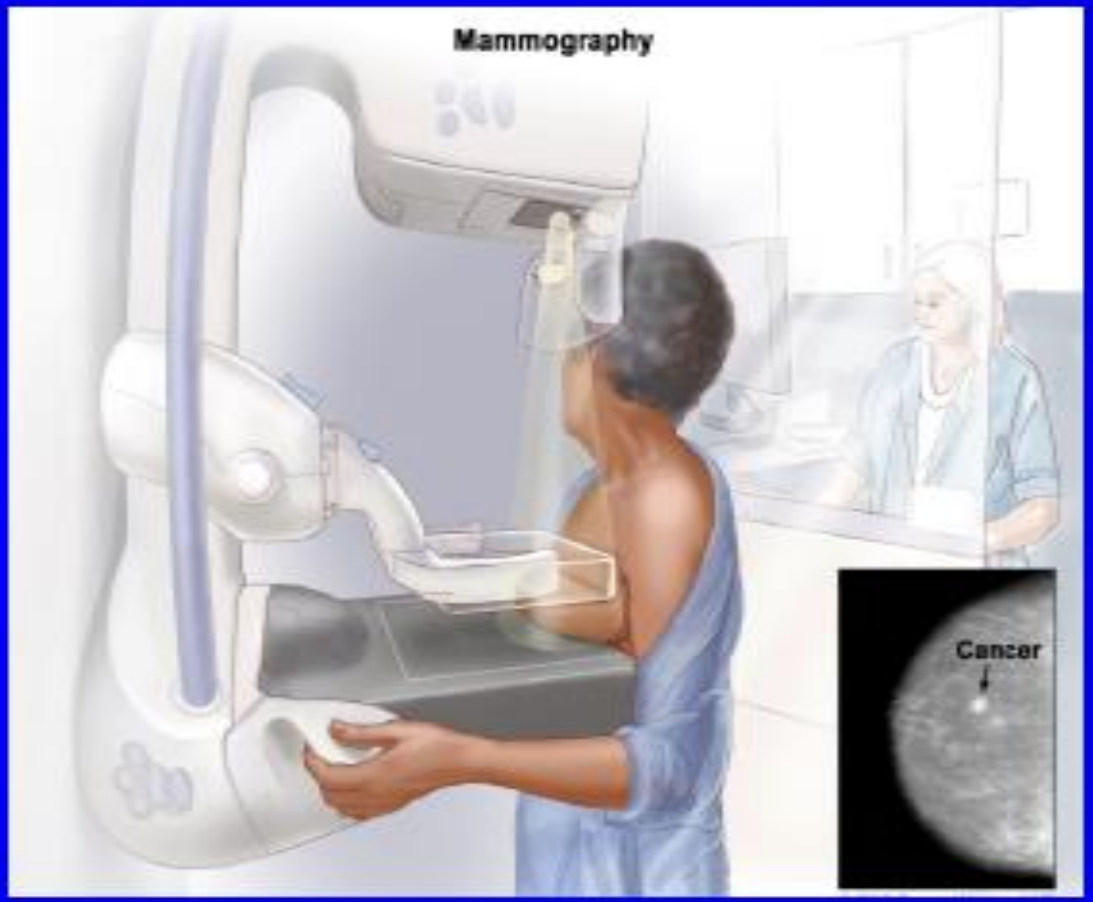
3 Types of Mammograms

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

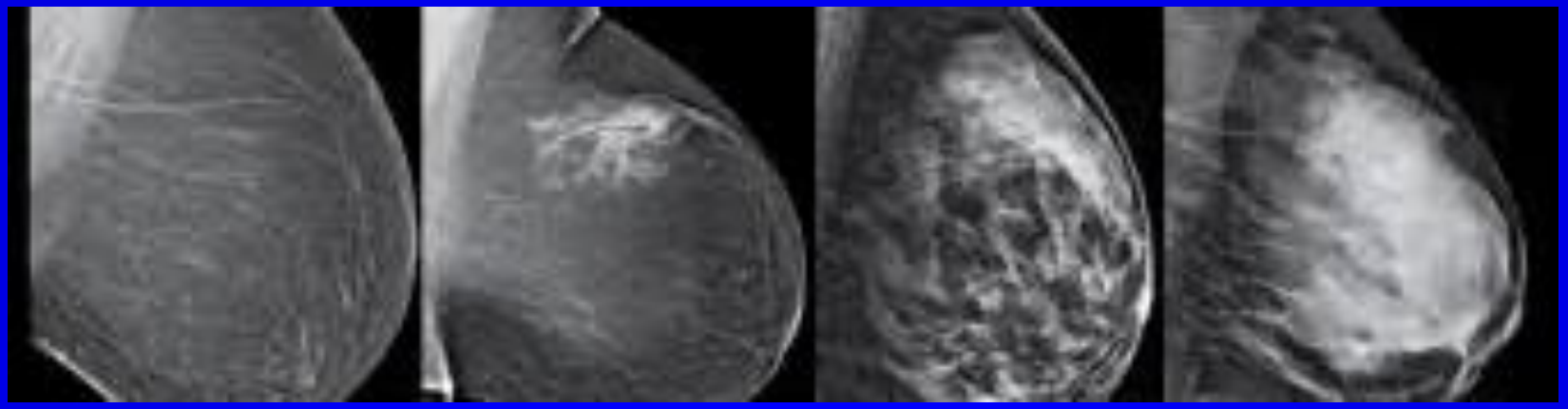
2. Digital Mammography
   - Computer Picture of the breast

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.



What Does it Mean to Have Dense Breast?



- Dense Breast Tissue is breast tissue that has a higher proportion of glandular and fibrous connective tissue than fatty tissue.
- On mammogram, dense tissue appears white, while fatty tissue appears black.
- Dense breasts are associated with an increased risk of breast cancer ONLY because it can make it harder for doctors to see abnormal growths on mammograms.

Having Dense Breast Tissue Does NOT mean you WILL get breast cancer!!!

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

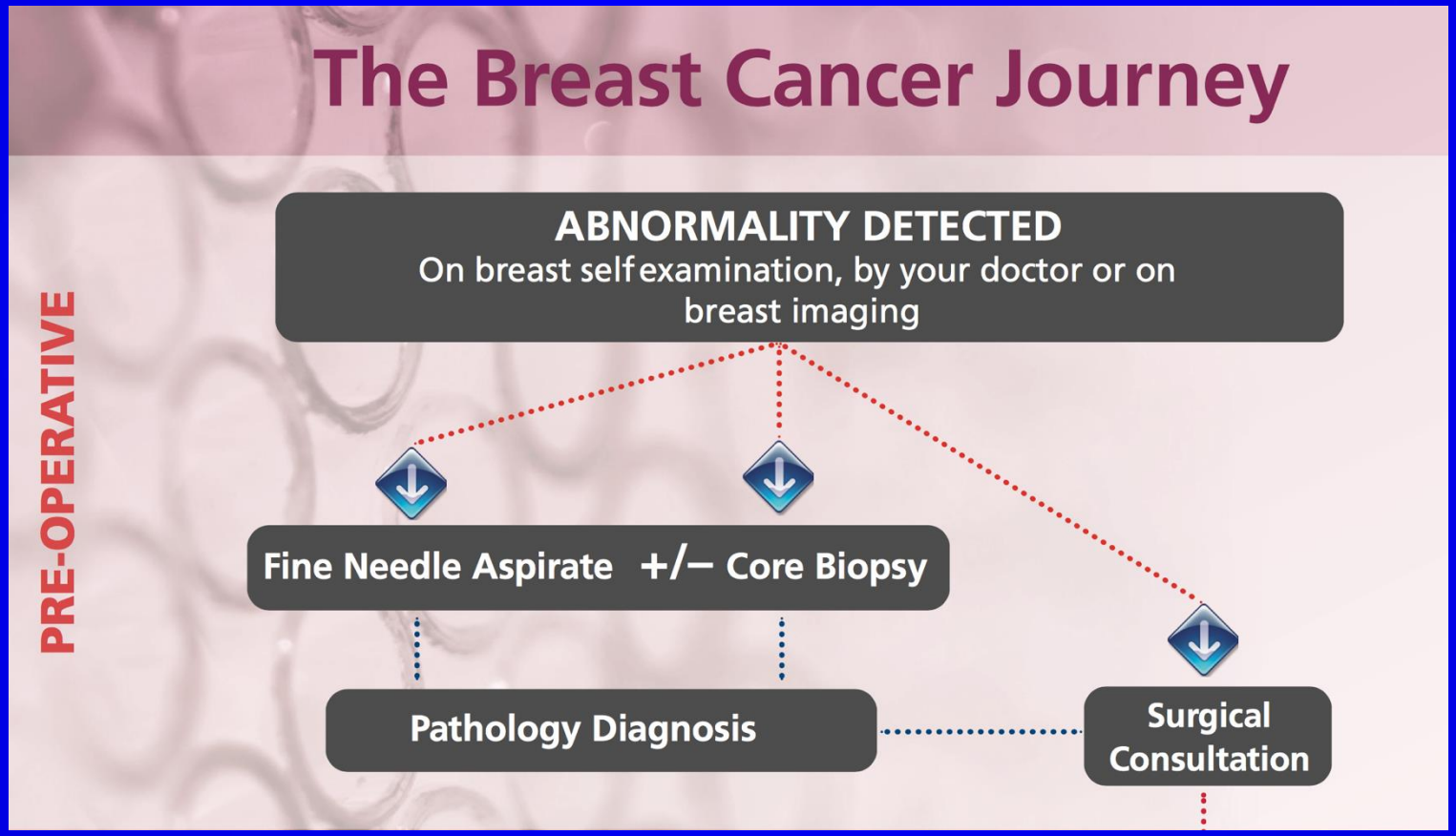
- Firm, smooth touch
- Fingers flat & together
- Circular Motion
- Follow a pattern
- Cover whole breast

Step 4

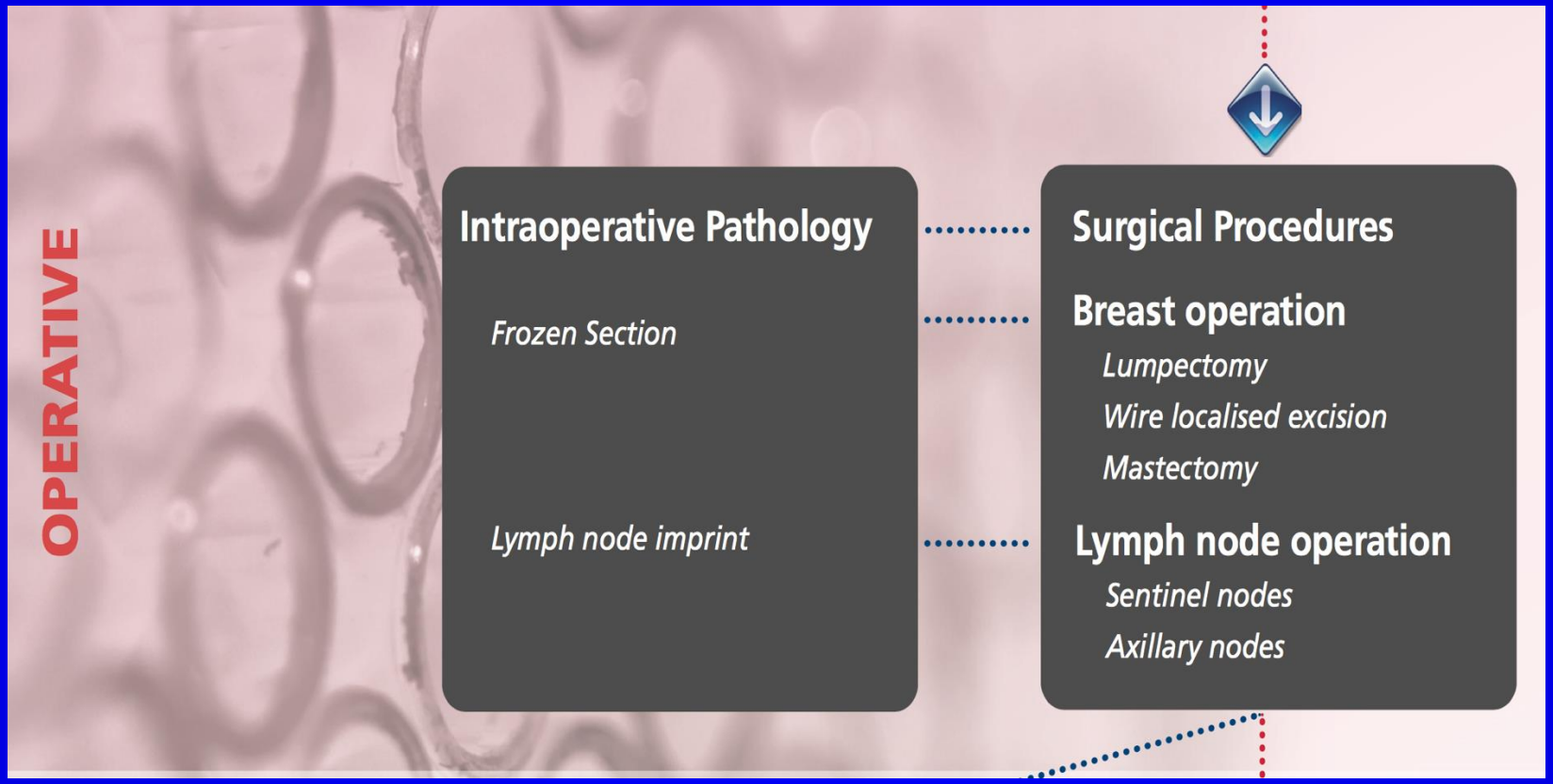
Examine upright

Patient journey

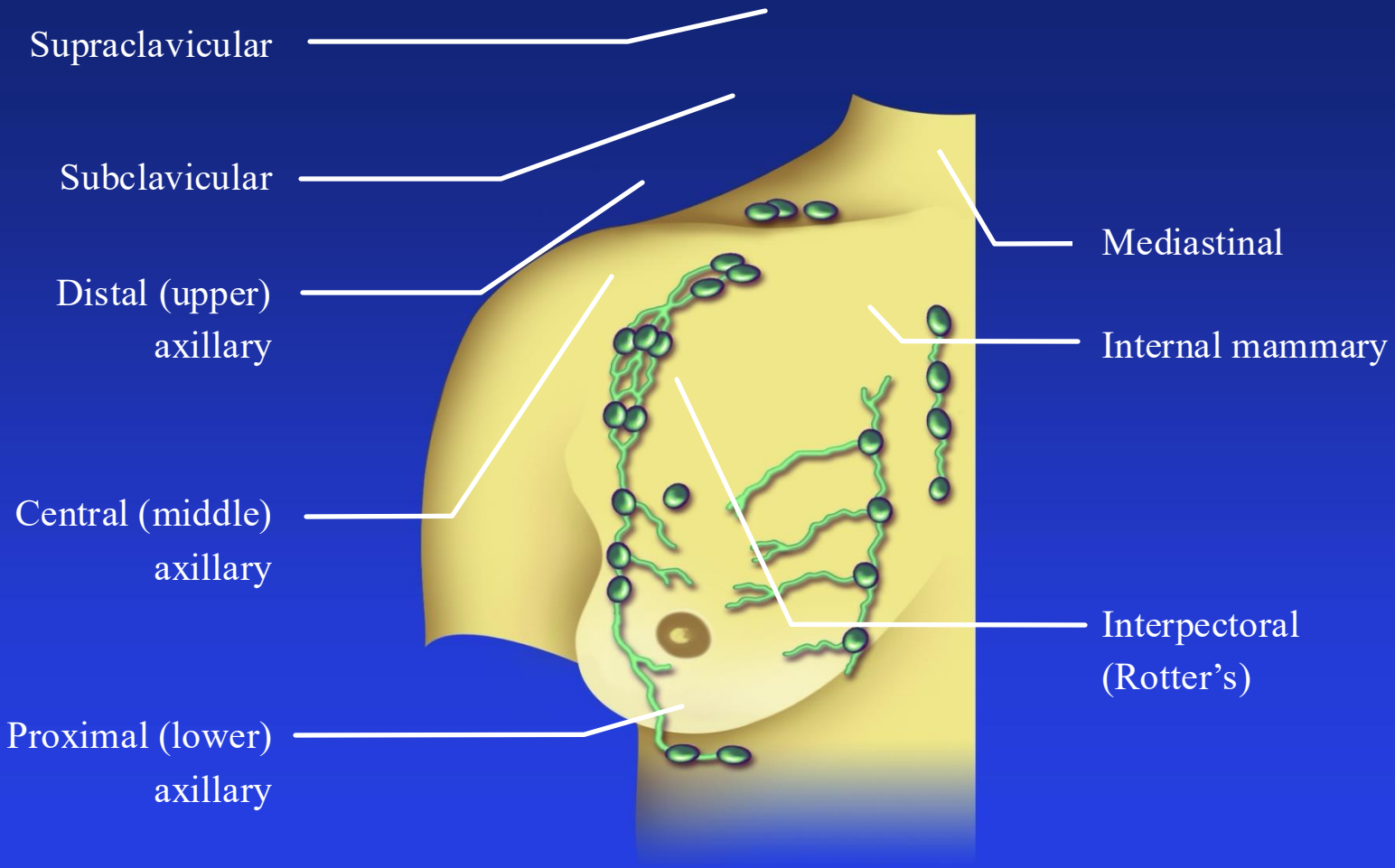
Pre-operative



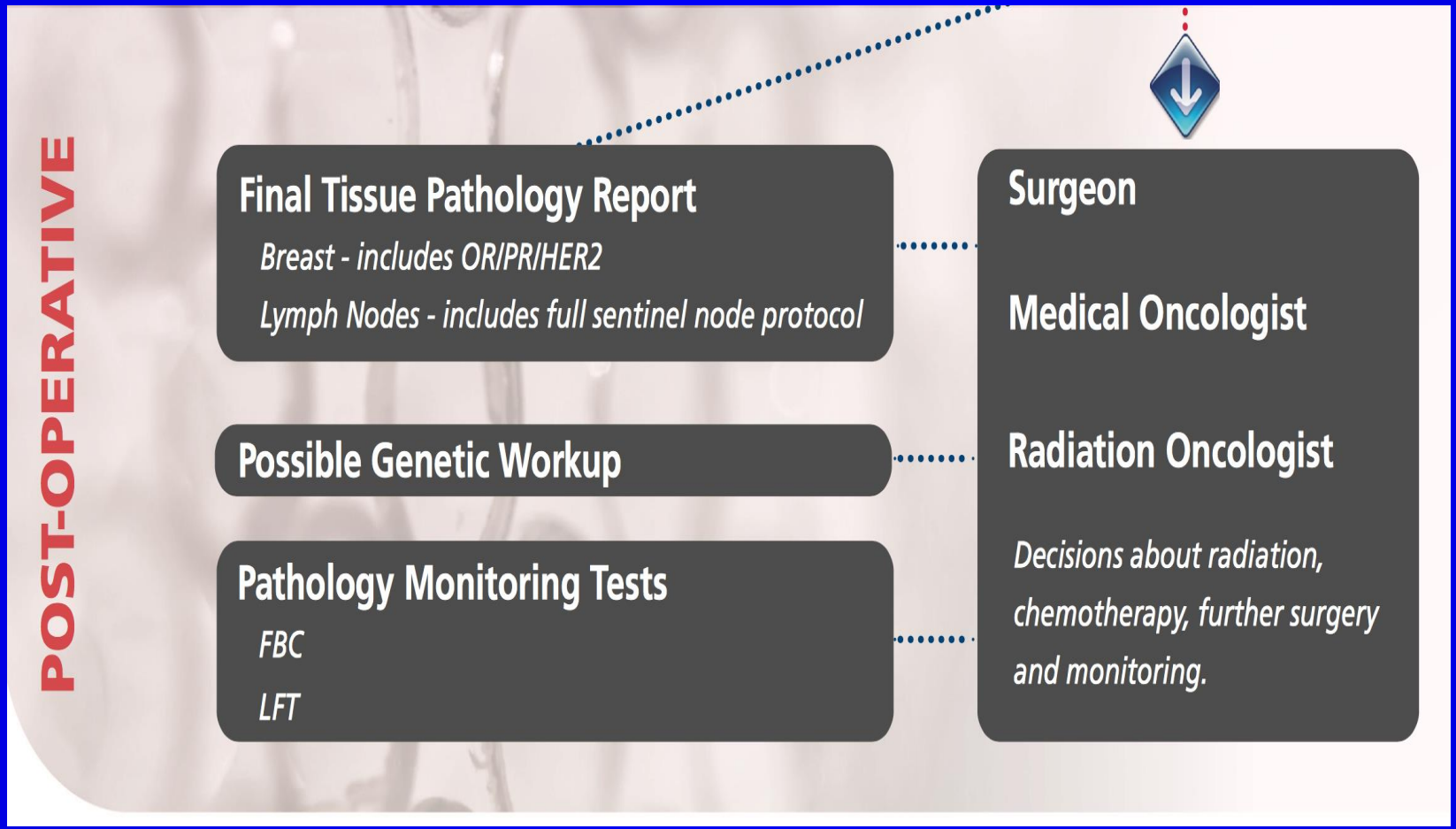
Operative


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

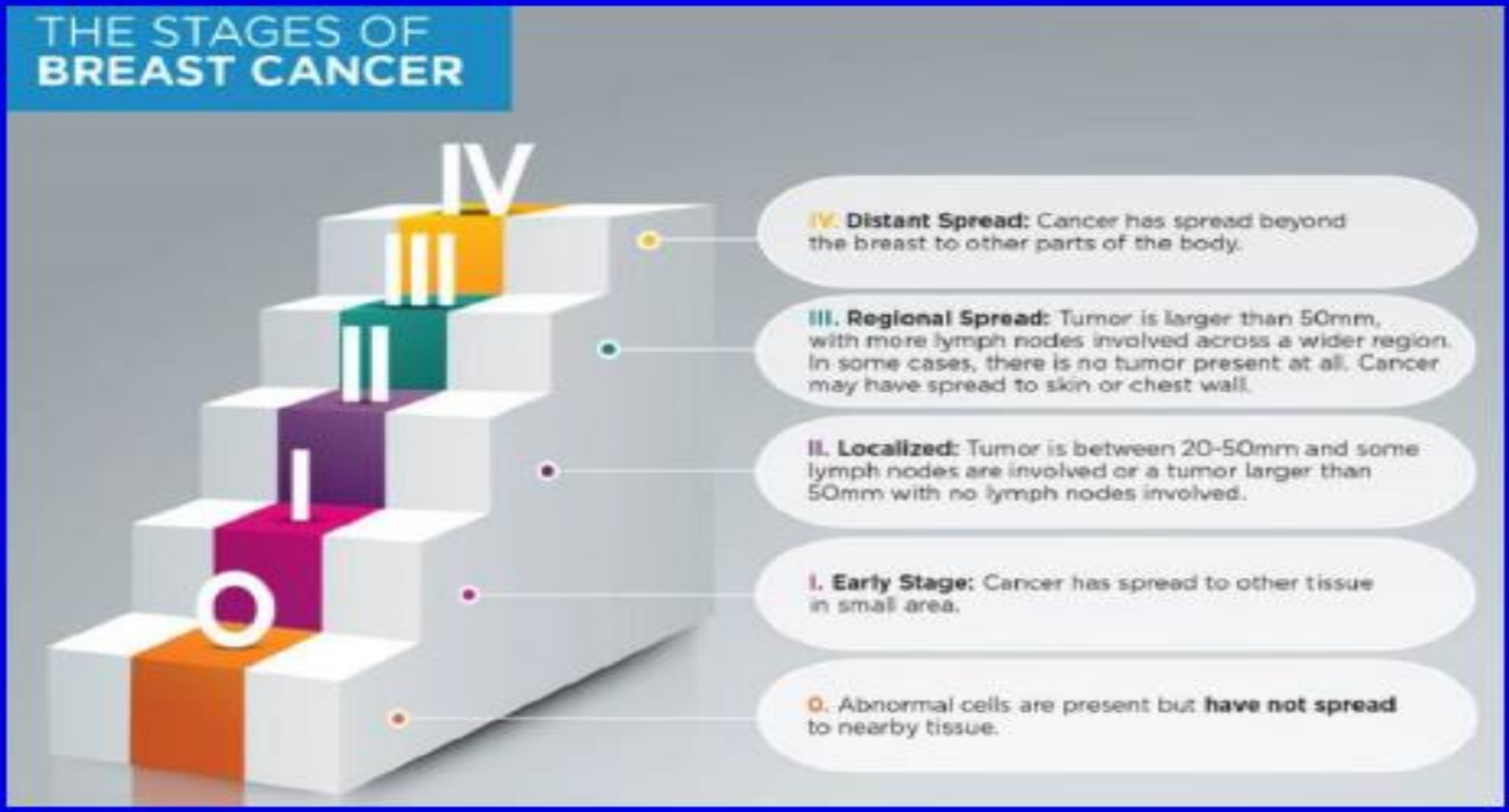
Structure of the Breast : Lymph Nodes



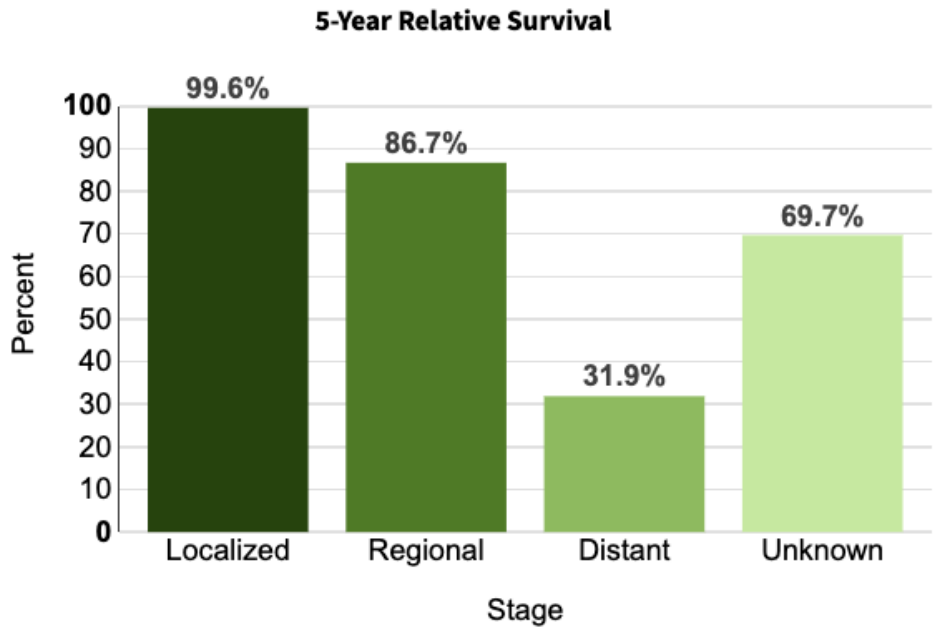
Post-operative



Breast cancer stages



5-Year Relative survival



SEER 22 (Excluding IL/MA) 2014–2020, All Races, Females by SEER Combined Summary Stage

Inflammatory Breast Cancer

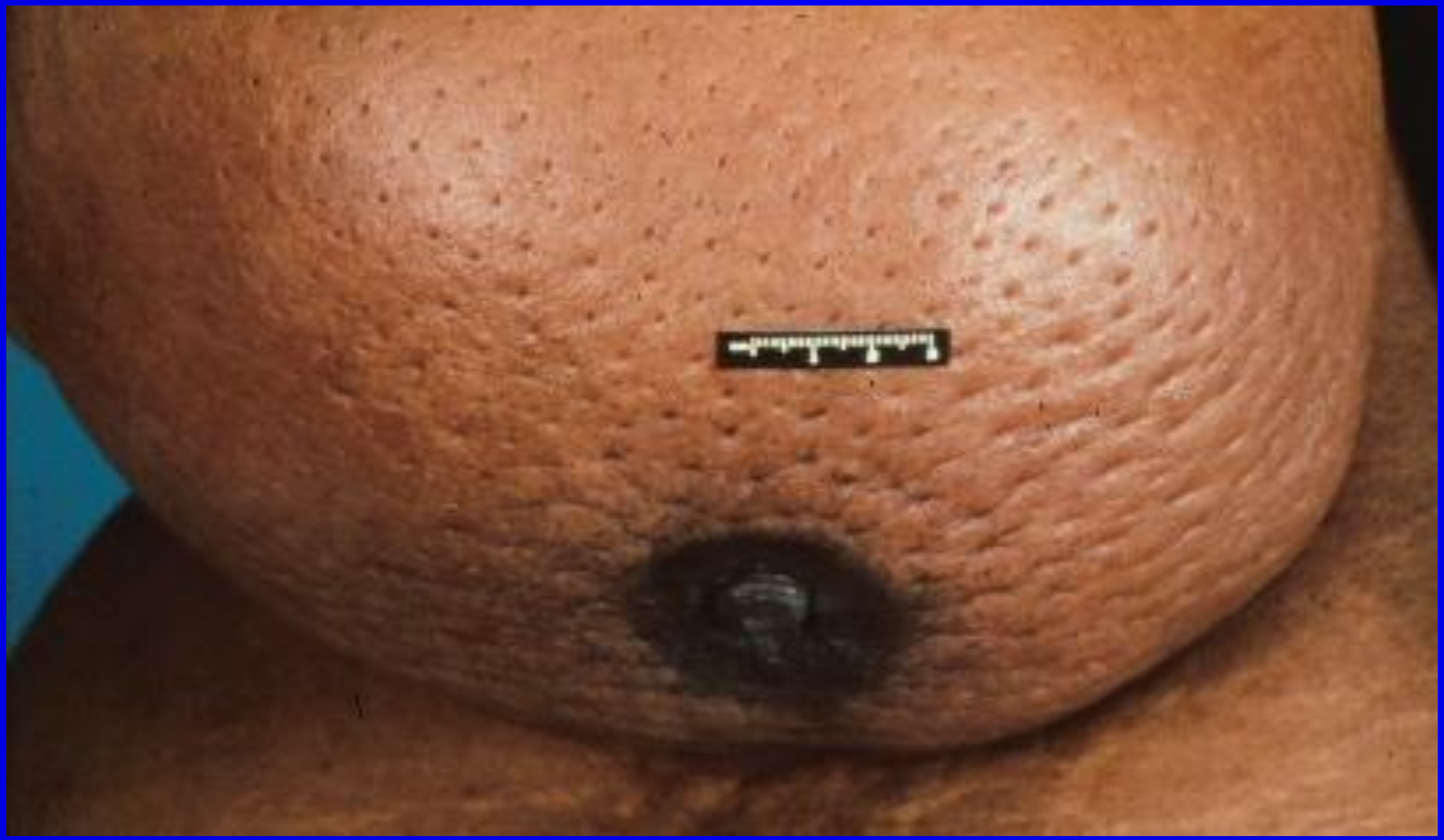
Definition

- 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

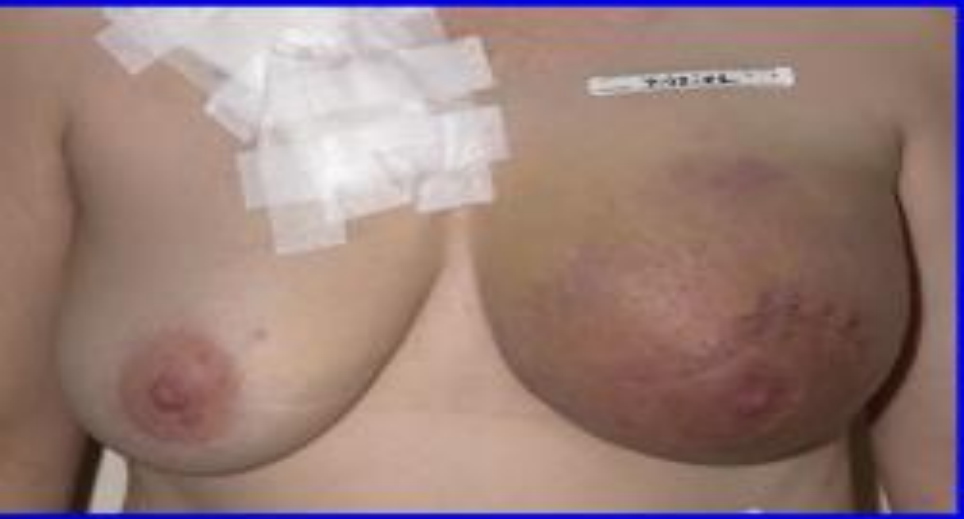
- Confirmed biopsy of invasive breast cancer .
- Rapid onset 3-6 months
- Erythema over ≥ 1/3 of the breast
- Edema (peau d'orange)
- Breast enlargement, often w/o a mass.

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

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

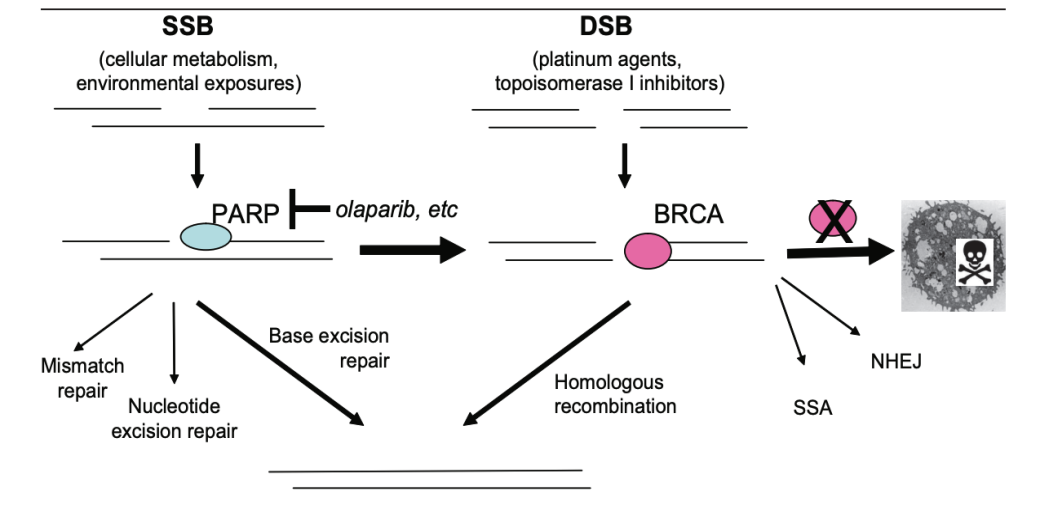
Molecular Profiling

- Presence of known mutations

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.
- Current research indicates assigning treatment based on specific mutations in breast cancer, particularly BRCA mutations, can significantly improve overall survival in both the early stage and metastatic setting, mainly through the use of targeted therapies like PARP inhibitors, which have shown effectiveness in patients with these mutations; however, the exact benefit depends on the specific mutation as well as the patient's individual tumor profile.
- With regard to other multiple mutations that can be found in tumors: it is often not clear which one to target to achieve maximal benefit. This is an avenue of ongoing investigation.

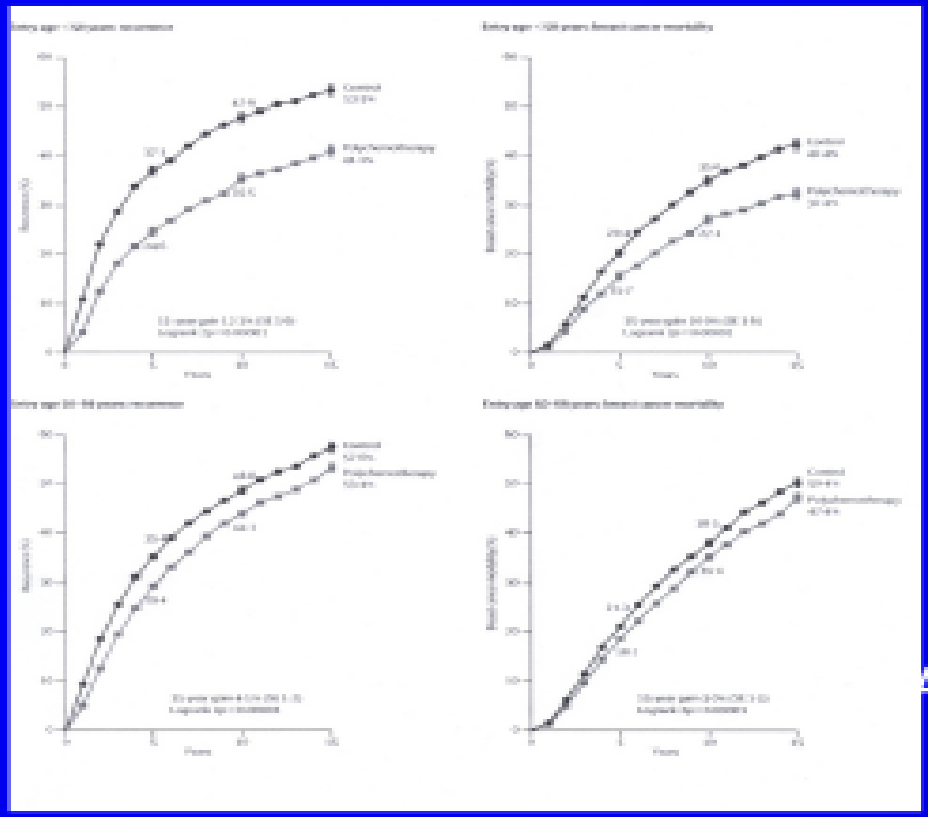
Mechanisms of Sensitivity to PARP Inhibition in BRCA-deficient cells



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

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*

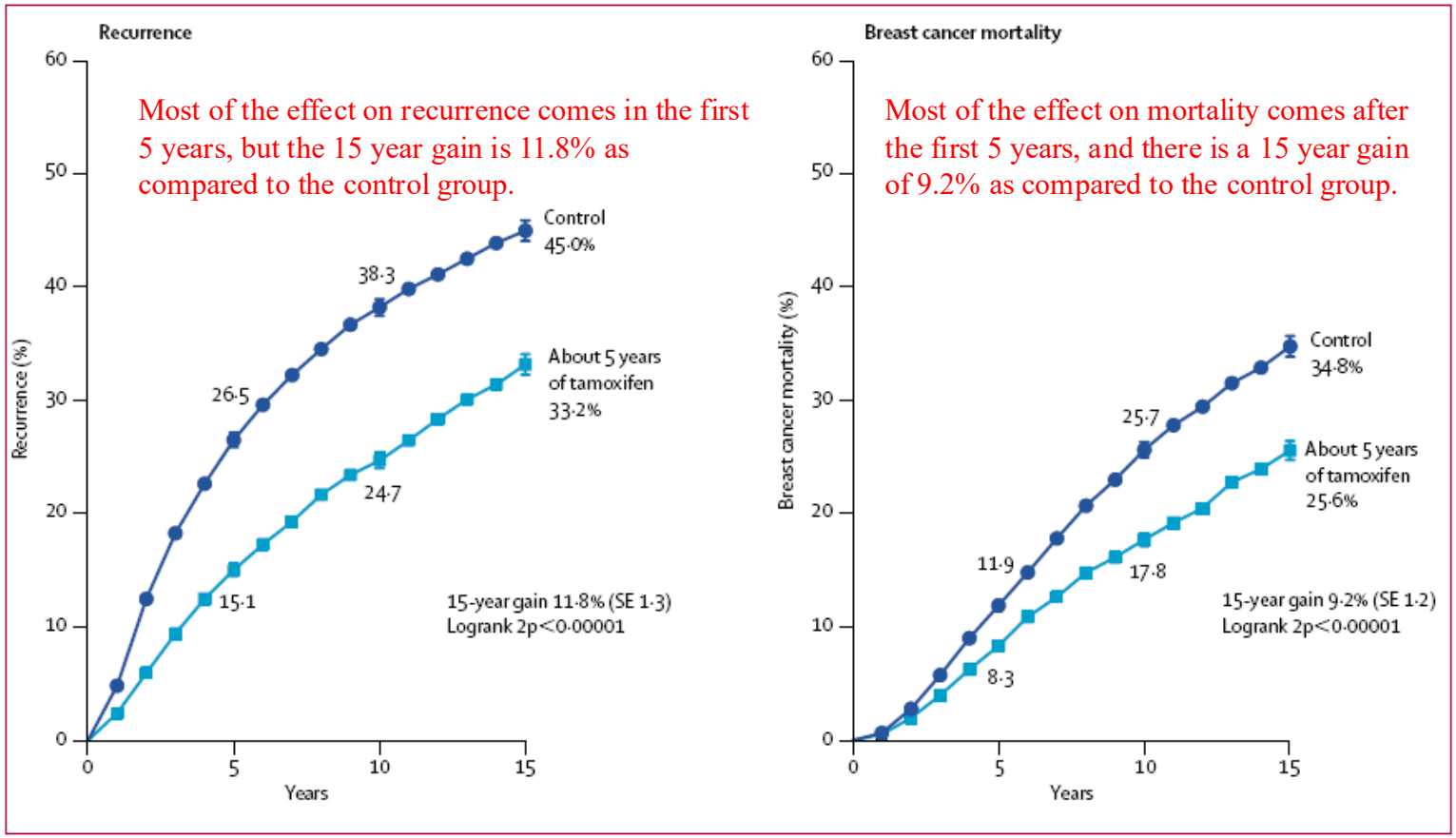
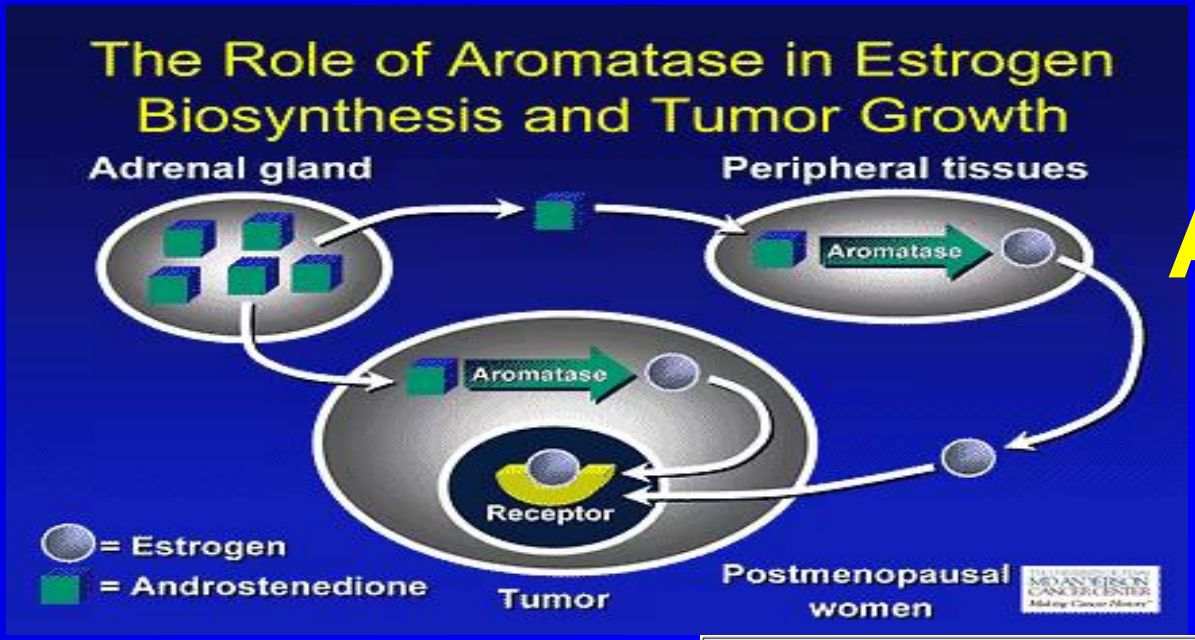


Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

At this point, it is worth mentioning:

In HR+ breast cancer (which is the most common subtype), the use of genomic assays to predict recurrence scores has markedly reduced the use of adjuvant chemotherapy, especially in patients older than 50 years of age.

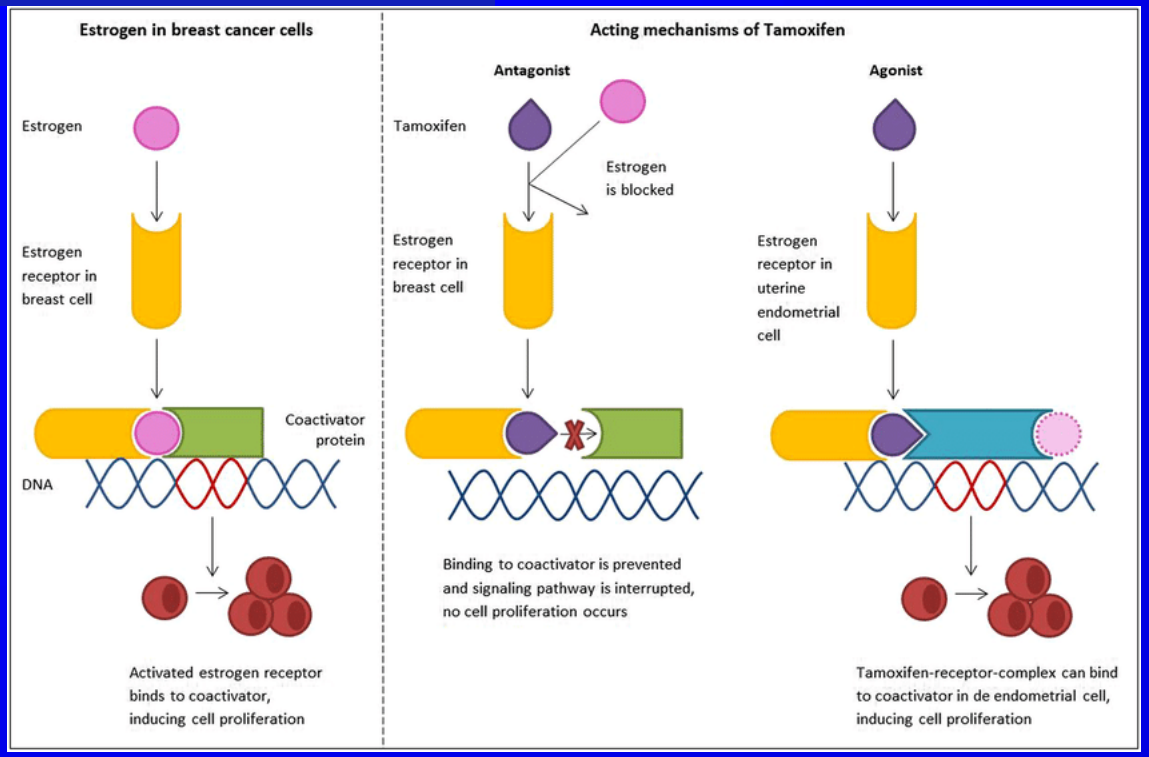
For patients with a lower recurrence score (0-25 for Oncotype DX) we have the option of treating with hormonal therapy alone, avoiding toxicity of chemo



Aromatase

Aromatase Inhibitors

Tamoxifen



Hormonal Therapies

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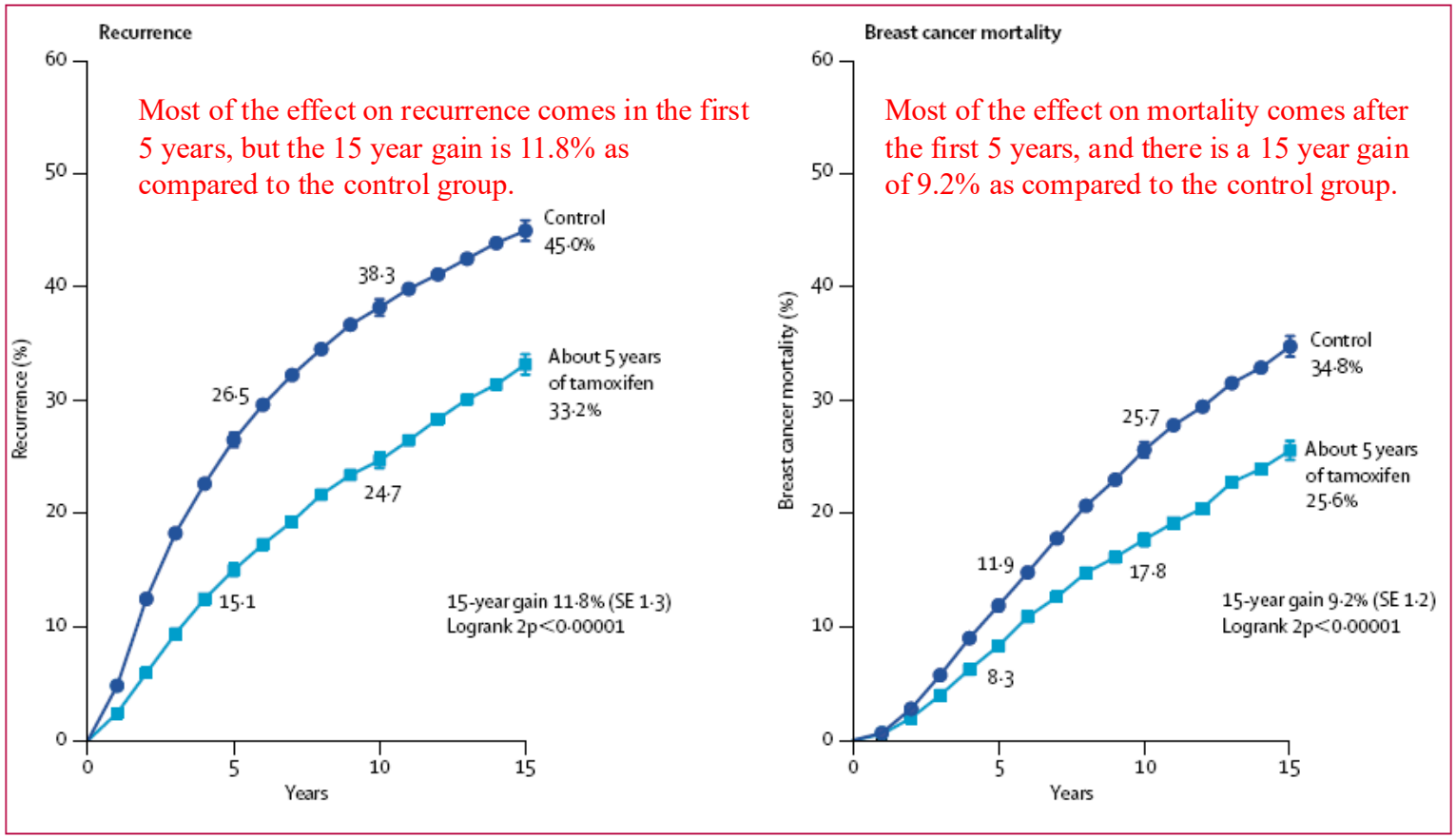
Exemestane	Aromasin	Post	Pill	Aromatase Inhibitor
Fulvestrant	Faslodex	Post	IM	Estrogen Receptor Antagonist
Goserelin	Zoladex	Pre	IM	Ovarian Suppression
Leuprolide	Lupron	Pre	IM	Ovarian Suppression

EBCTCG: Benefit of Tamoxifen as Adjuvant *Treatment*



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10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

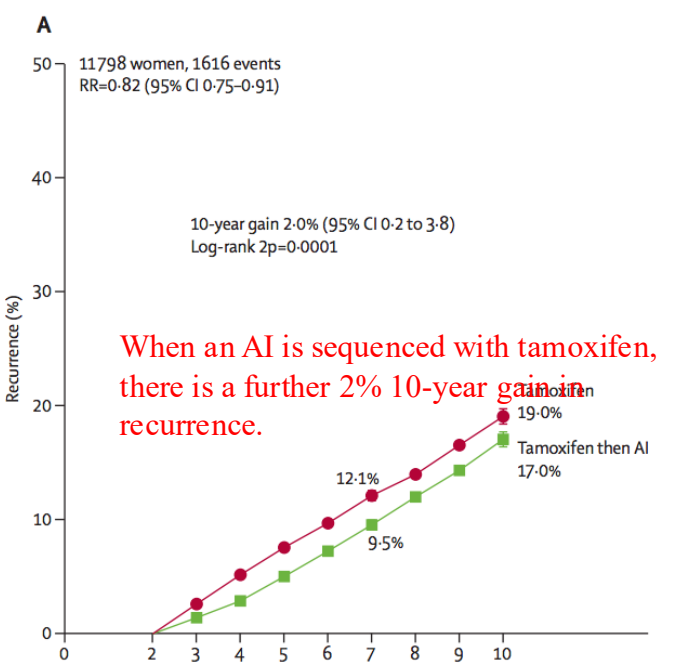
EBCTCG, Lancet 2005,365: 1687

EBCTCG

Lancet, 2014

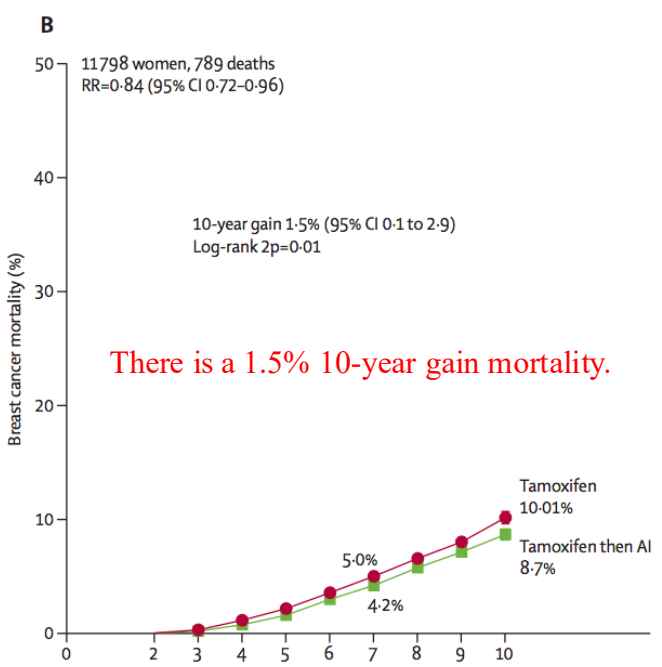
Tamoxifen followed by AI in Adjuvant Setting

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

At this point it is worth mentioning:

Aromatase inhibitors remain the optimal endocrine therapy in post-menopausal women with HR+ early-stage breast cancer.

Additionally, in pre-menopausal women, two trials with long-term follow up data that matured in 2022 (SOFT and TEXT) demonstrated a benefit for ovarian suppression along with an aromatase inhibitor rather than tamoxifen alone.

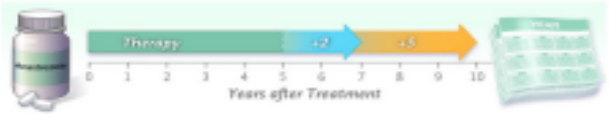
However, questions remain regarding the optimal management of HR+ disease in younger patients and in those who are high risk enough to justify chemotherapy and whether ovarian function suppression can be substituted for chemotherapy in some of those patients.

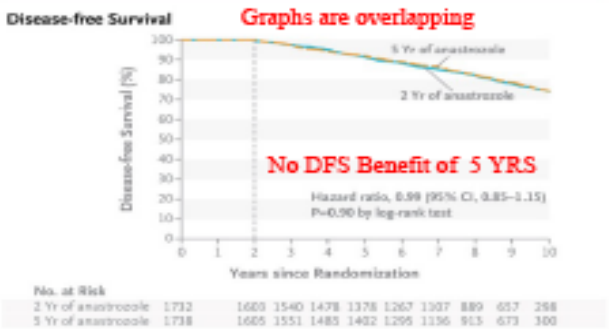
- **A meta-analysis was presented at the 2023 ASCO Annual Meeting included 15, 000 women from 23 trials and demonstrated a benefit of ovarian suppression regardless of receipt of chemotherapy.**

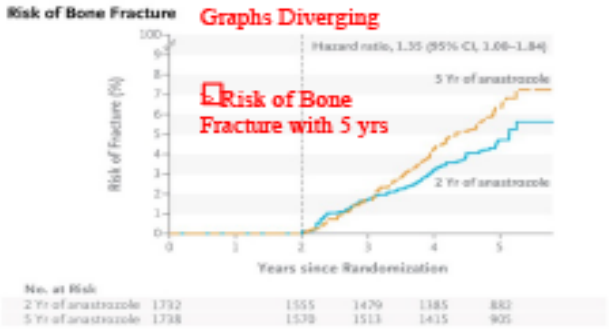
- **The study showed that women who did not receive chemotherapy or who remained pre-menopausal after chemotherapy had an almost 10% decrease in the risk of recurrence at 15 years when they received ovarian suppression, and they also had a significant improvement in breast-cancer related and overall survival.**

- **Patients who received chemotherapy and had an unknown menopausal status after treatment achieved only a minimal benefit of the addition of ovarian suppression.**

Aromatase inhibitor

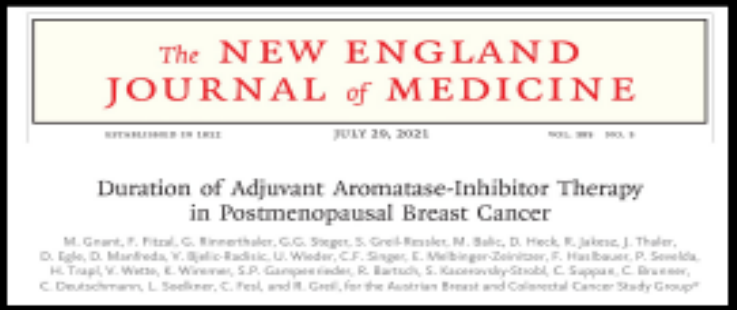






CONCLUSIONS

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:

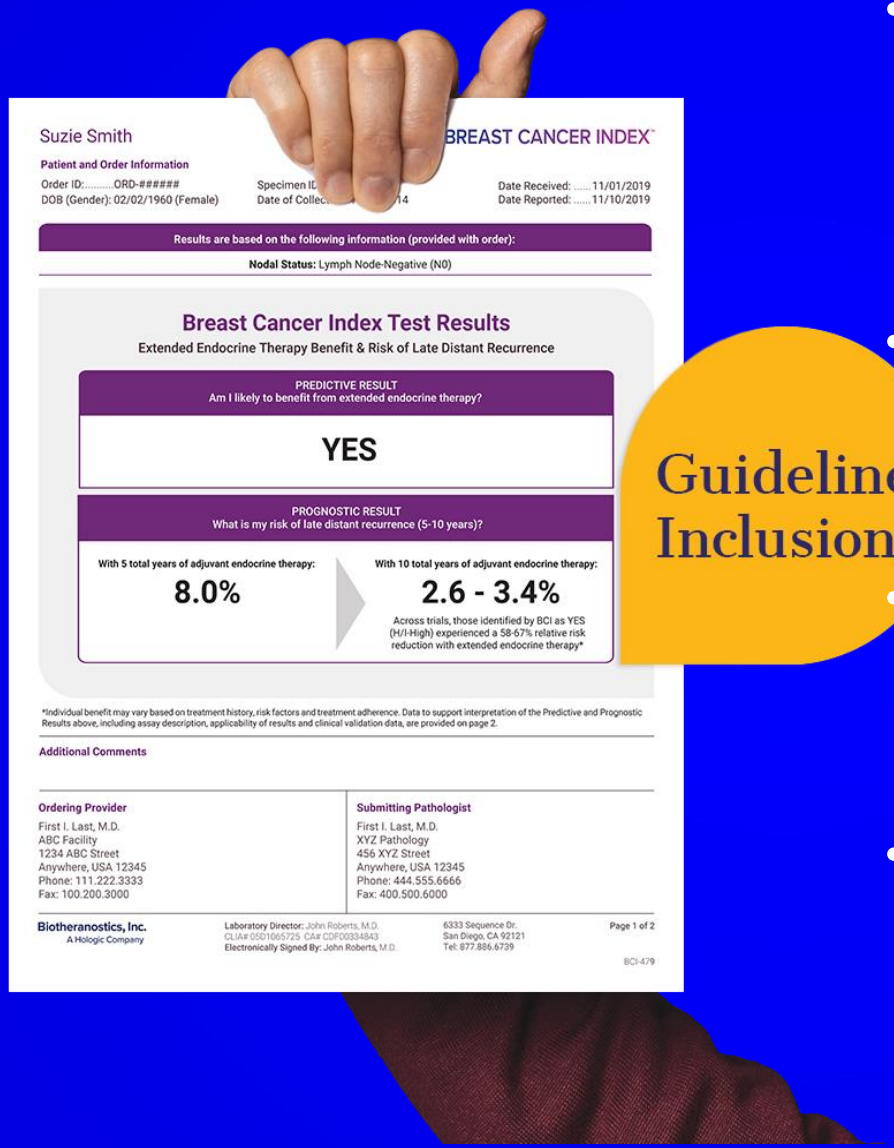
- Extending HR therapy by 5 years provided no benefit over a 2 year extension, but was associated with a greater risk of bone fracture.

Breast cancer index (BCI)

- **NCCN Clinical Practice Guidelines in Oncology** (NCCN Guidelines®) and the **American Society of Clinical(BCI Oncology®** (ASCO®) now recognize the Breast Cancer Index® (BCI) as the only genomic test that can predict the benefit of extended endocrine therapy in early-stage, HR+ breast cancer.
- That means avoiding potential overtreatment of patients for whom endocrine therapy beyond 5 years is unlikely to provide benefit, as well as informing treatment for the patients it may help.

"The HOXB13/IL17BR (BCI) ratio remains the only biomarker that has demonstrated significant treatment interaction for prediction of extended endocrine therapy benefit, earning guideline inclusion earlier this year."

Guideline inclusion



Guideline Inclusion

- Top part of report will give a simple YES or NO whether extended adjuvant therapy will benefit a patient.
- Bottom left indicates risk of late distant recurrence with 5 years of therapy
- Bottom right shows risk of late distant recurrence with 10 years of therapy.
- The BCI was also shown to be prognostic in premenopausal women with HR+ breast cancer enrolled in the SOFT trial. A low H/I ratio was predictive for the benefit of ovarian suppression.

Fertility

- Fertility preservation is a driving concern for many young women with breast cancer.
- Many of these women have HR+ breast cancer and are treated from 5-10 years with adjuvant endocrine therapy, which is known to compromise fertility.
- The early results of the POSITIVE Trial (reported NEJM March 2023) may be reassuring.
- In this international single arm trial, women were allowed to discontinue endocrine therapy for up to 2 years to attempt pregnancy.
- Results indicated that this appeared to be safe over short-term follow up (41 months), with 86% of those who became pregnant having at least one live birth, with a 3-year rate of recurrence of 8.9% (recurrence rate compared to "control" from SOFT and TEXT

- **Fertility Preservation**

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
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.

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*

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

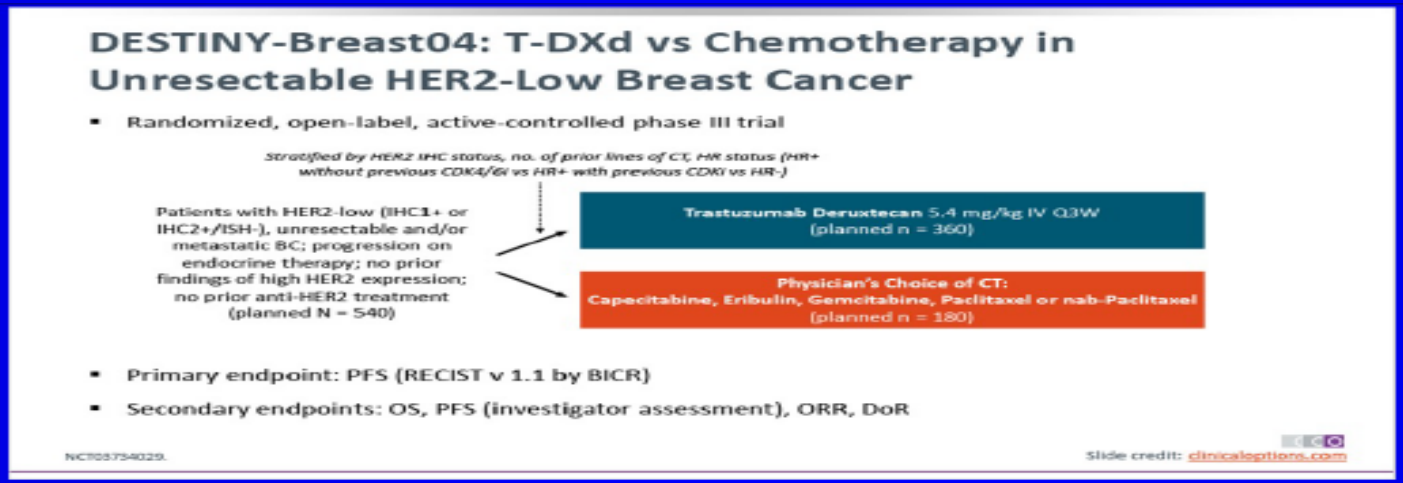
News-Maker 2022!!

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,

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.**

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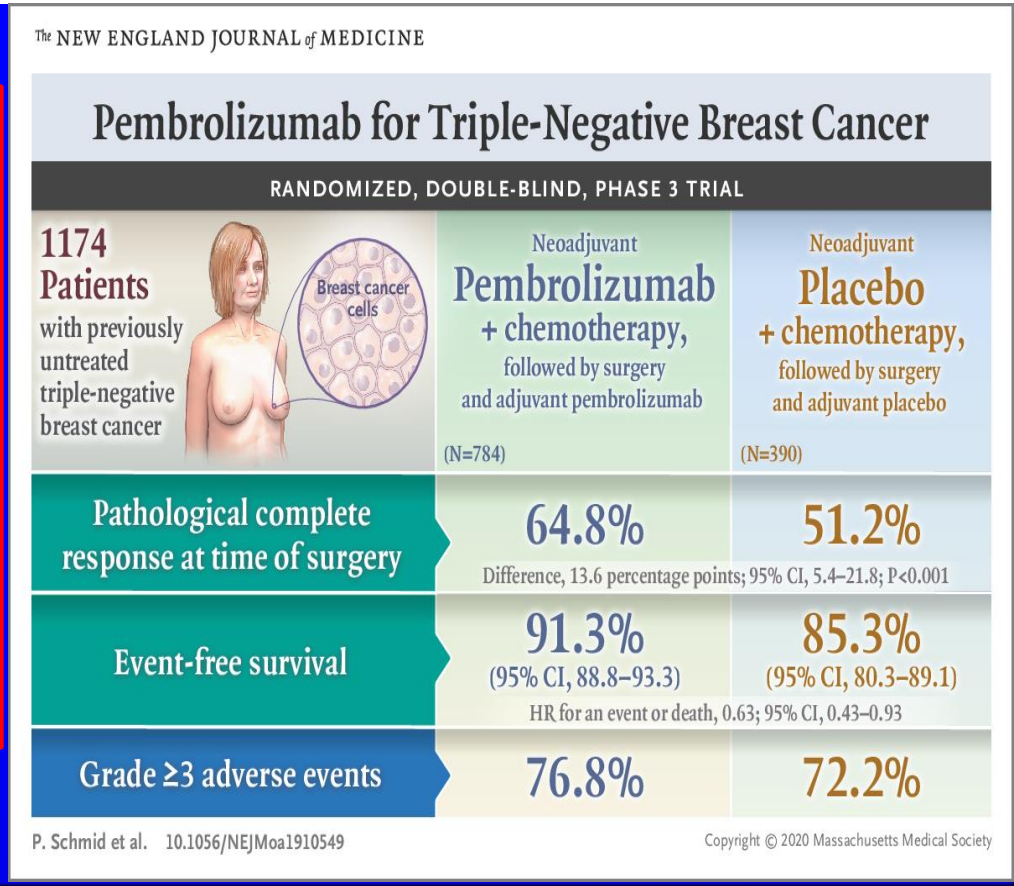


Treatment

MYTH:

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

FACT:

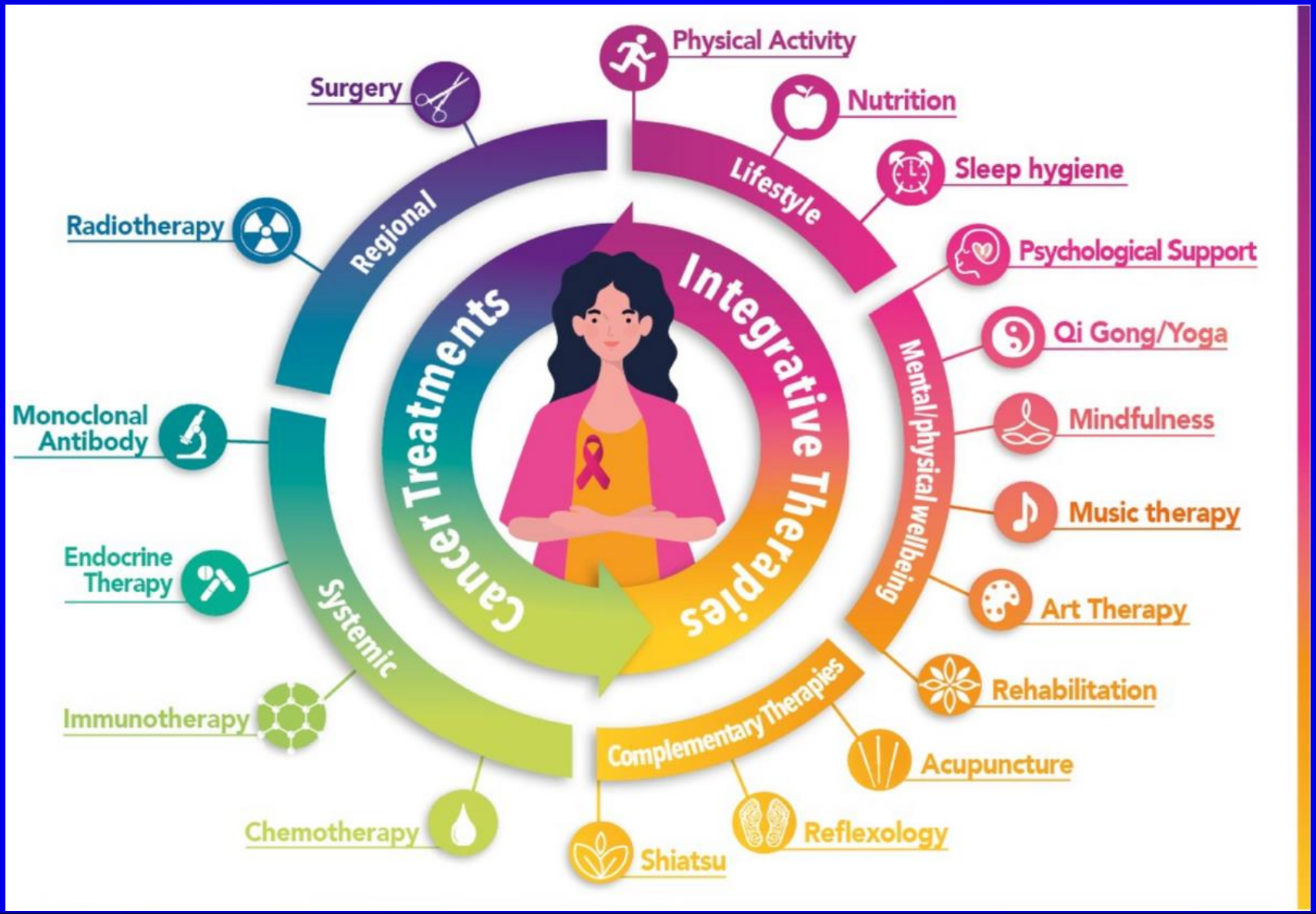
Breast Cancer can have long-term impact on people's lives and well-being.

- 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.

Patients

- 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 Bio-psycho-social Perspective on Medicine, and learn to treat the whole patient, and not just the disease.
- 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.

Integrated Care Approach
Improving Well-Being in Cancer Patients



Thank you