Metastatic Breast Cancer Overview

This presentation was developed by Lilly Medical and is intended to be used by HCPs for medical, scientific and educational purposes.

Objectives

- Provide an overview of the breast cancer disease state
- Describe the epidemiology and anatomy of breast cancer
- Discuss different types and stages of breast cancer
- Elaborate on metastatic breast cancer and its subtypes
- Summarize treatment options for metastatic breast cancer

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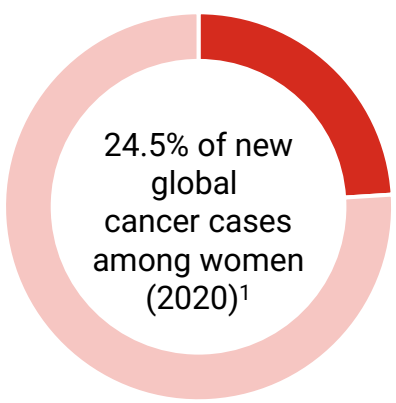
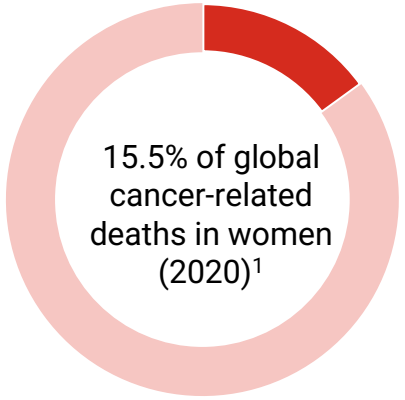
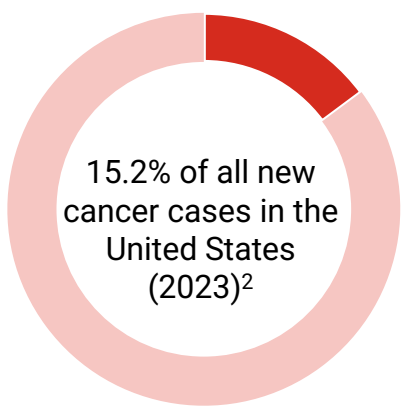
Breast Cancer: Incidence and Mortality Rates

Breast Cancer Accounts for:







- About 2.3 million (11.7%) new cases of breast cancer were reported globally among women in 2020[1]
- Breast cancer is the most commonly diagnosed carcinoma and leading cause of tumor-related deaths among women worldwide[1]
- Although rare, men can also develop breast cancer[3]
- Fewer than 1% of breast cancer cases are reported in men in the US[3]

1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249. 2. https://seer.cancer.gov/statfacts/html/breast.html (Accessed Oct. 27, 2023). 3. https://www.breastcancer.org/types/male-breast-cancer (Accessed Oct. 27, 2023).

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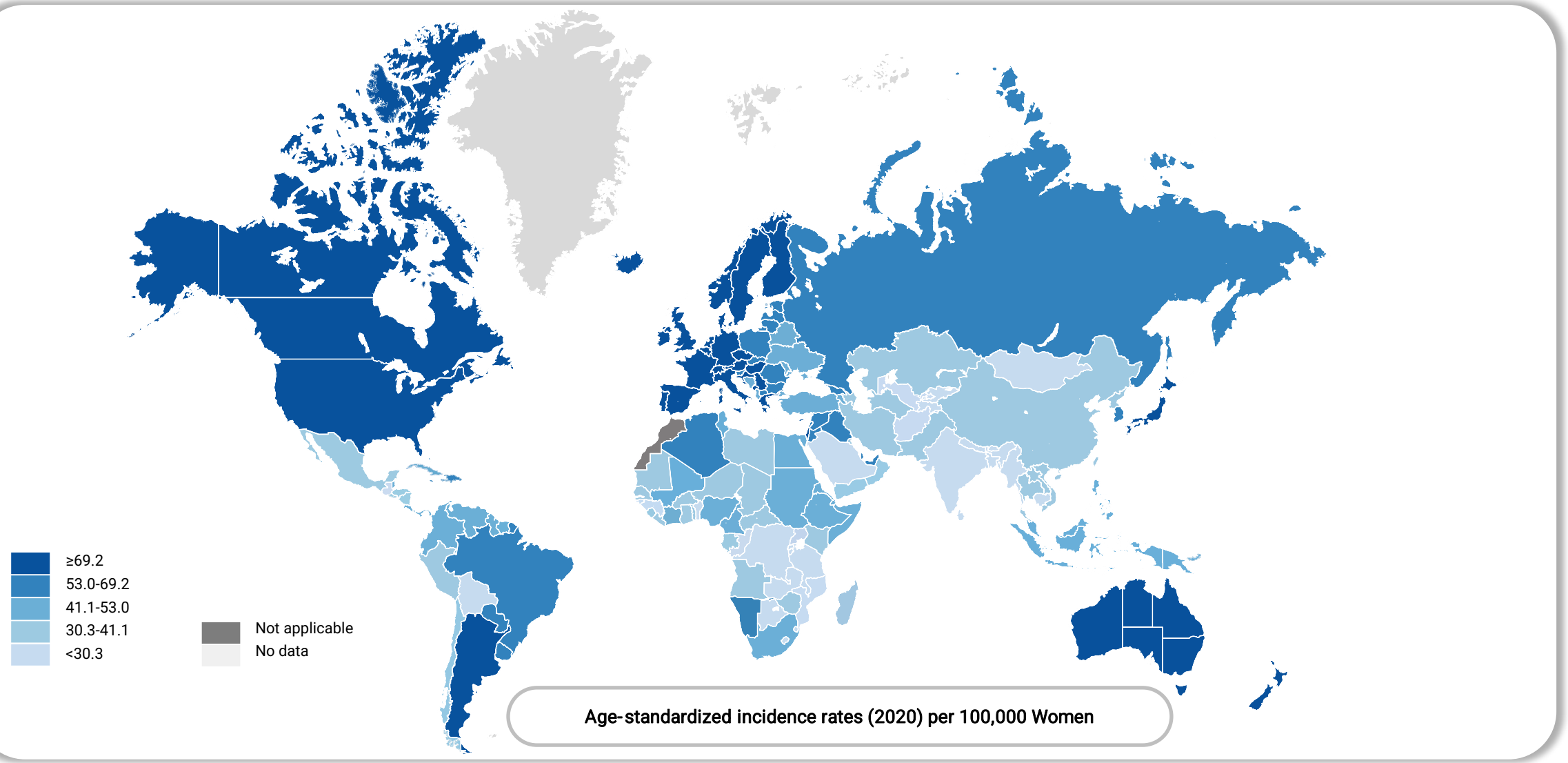
Breast Cancer: Global Epidemiology



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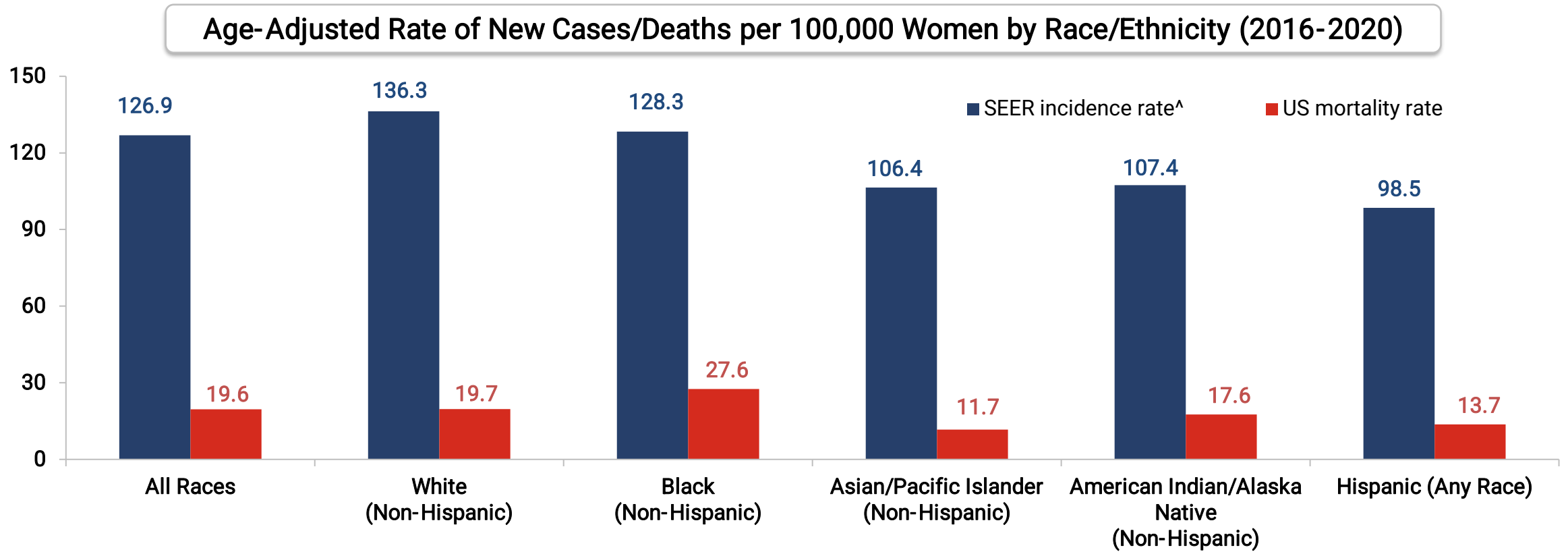
SEER Breast Cancer Incidence and US Mortality Trends



- Incidence rates are higher among white, non-Hispanic women.
- Mortality rate remains higher in Black (Non-Hispanic) women.

^Please refer to the speaker notes. SEER=Surveillance, Epidemiology, and End Results. https://seer.cancer.gov/statfacts/html/breast.html (Accessed Oct. 27, 2023).

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Anatomy of the Breast

- A female breast has no muscle tissue, but has a layer of fatty tissue surrounding the breast glands and extends throughout the breast.[1]
- Each breast has 3 main components: lobules, ducts, and connective tissues.[1]
- **Lobules**:
  - Each breast contains 15-20 lobes.[1]
  - Each lobe has several lobules, at the end of which are tiny bulb-like glands, or sacs, where milk is produced in response to hormones.[1]
- **Ducts:** Connect the lobes, lobules, and glands. In nursing mothers, these ducts deliver milk to openings in the nipple.[1]
- **Most breast cancers originate in the cells that line the ducts, and a few originate in the lobules.**[2-4]

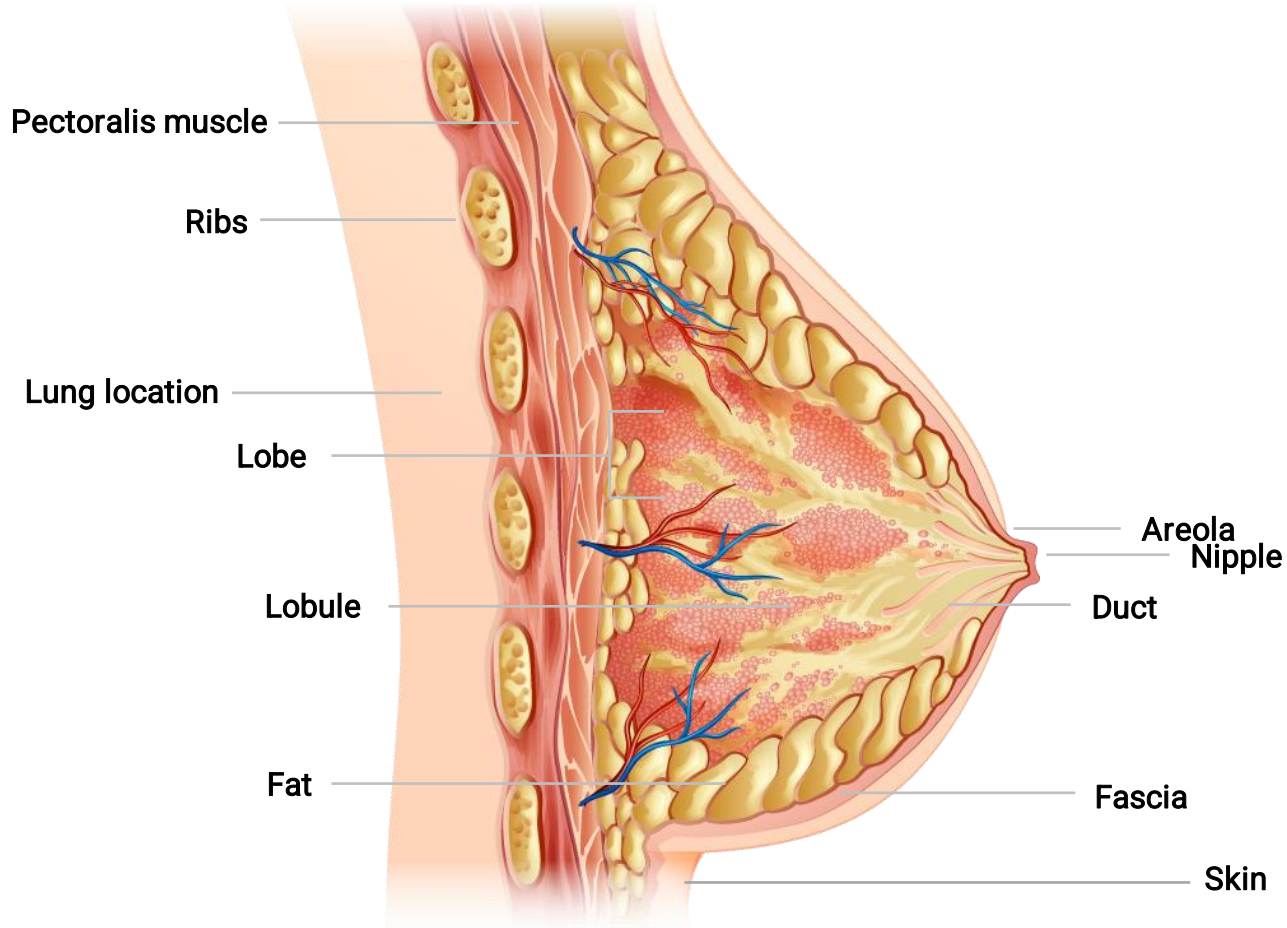

Image is labelled as per reference 1. 1. https://training.seer.cancer.gov/breast/anatomy/ (Accessed Oct. 27, 2023) 2. CDC-What Is Breast Cancer? (Accessed Oct. 27, 2023) 3. https://institut-curie.org/dossier-pedagogique/not-one-breast-cancer-many (Accessed Oct. 27, 2023) 4. Mayo Clinic-Breast cancer types-What your type means? (Accessed Oct. 27, 2023)

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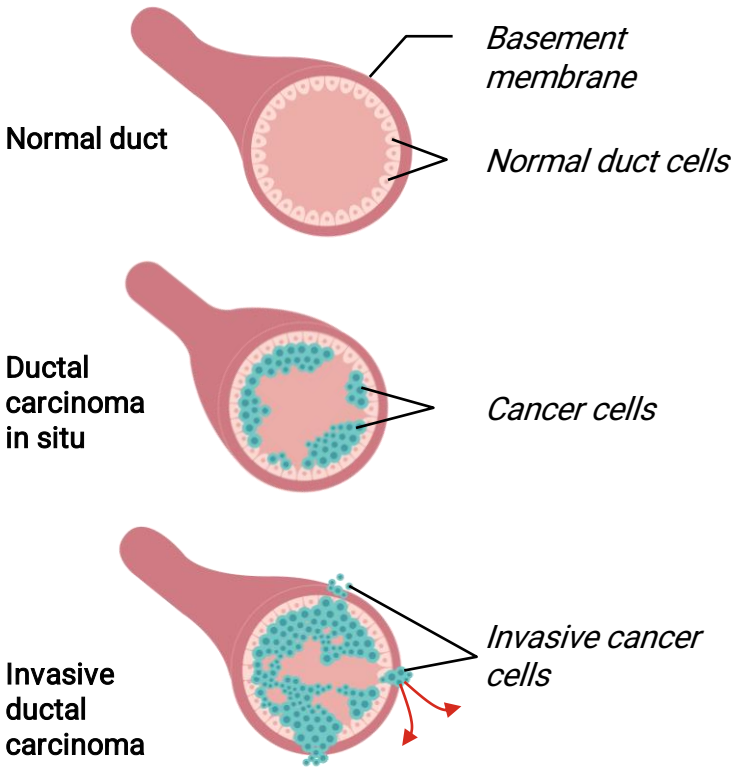
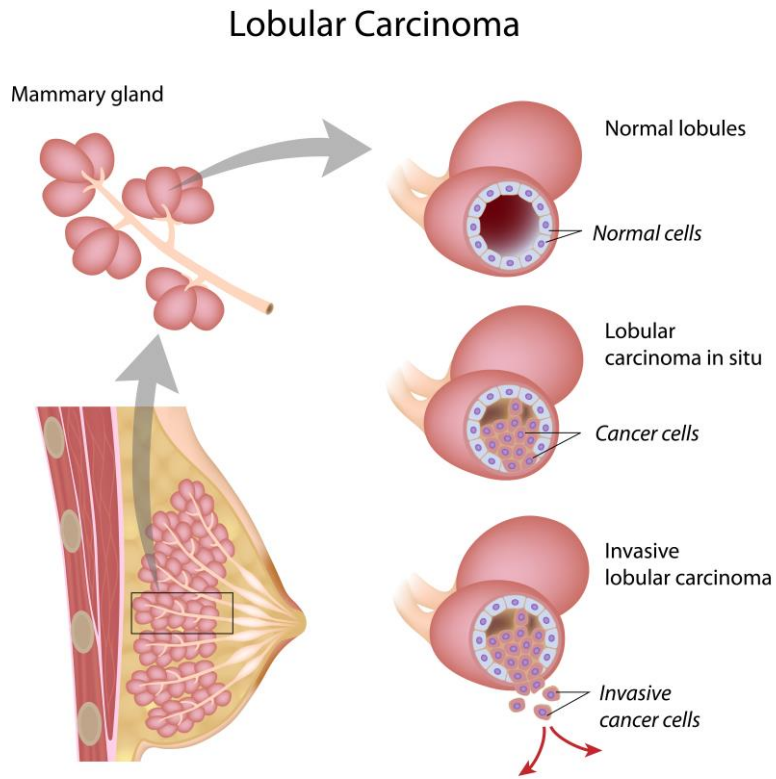
Breast Cancer: Classification

Invasive Ductal Carcinoma (~75% in the US)[4]



- **Invasive Ductal Carcinoma**[1,2] – Infiltrating (spreading); most common type of all breast cancer cases; can spread to other parts of the body, including lymph nodes
- **Invasive Lobular Carcinoma**[1,3] – Second most common type of all breast cancer cases; cancer begins in the lobules and can also spread to other parts of the body.

Invasive Lobular Carcinoma (~10% in the US)[4]



1. CDC-What is Breast Cancer? (Accessed Oct. 27, 2023). 2. https://www.breastcancer.org/types/invasive-ductal-carcinoma (Accessed Oct. 27, 2023). 3. https://www.breastcancer.org/types/invasive-lobular-carcinoma (Accessed Oct. 27, 2023). 4. Feng Y, et al. *Genes Dis.* 2018;5(2):77-106.

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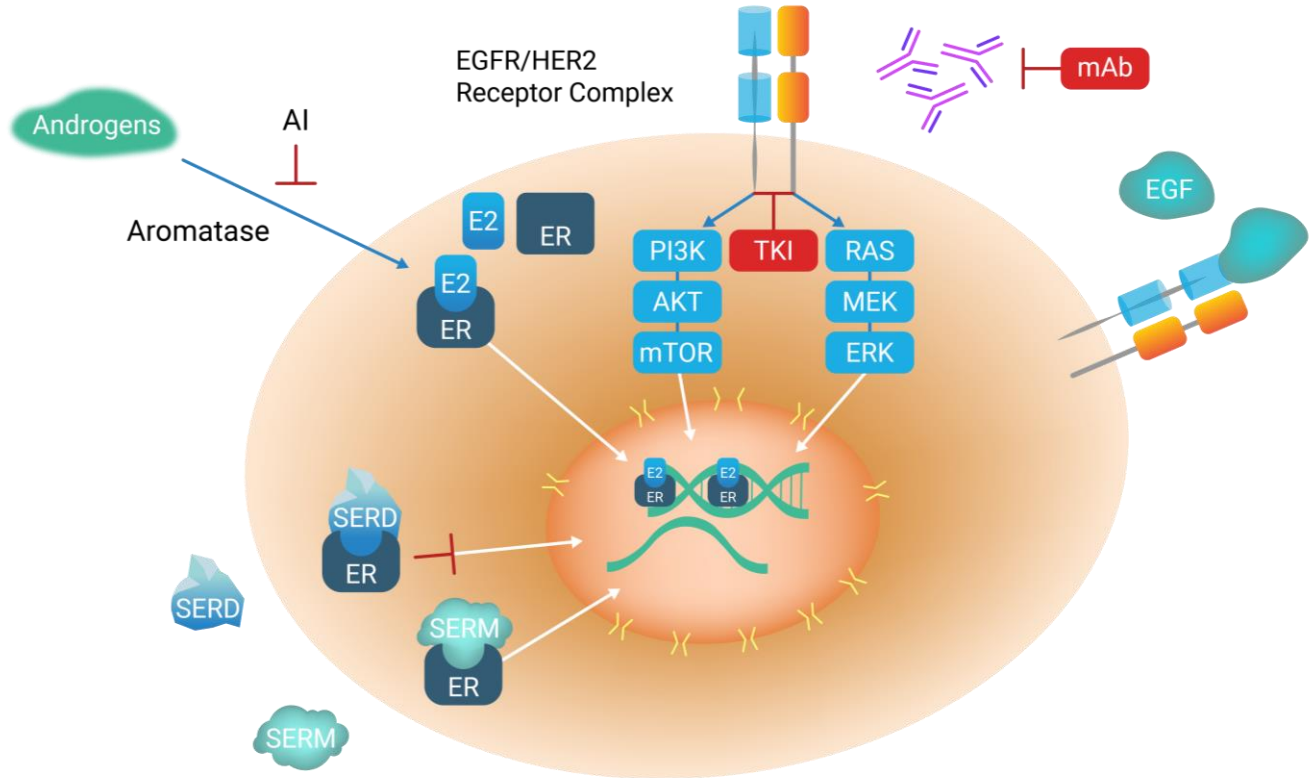
Hormone Receptors

Estrogen/Estrogen Receptor (ER) and Progesterone Receptor (PR):

- Estrogen, a sex steroid hormone produced by ovaries, plays a role in the growth, differentiation, and function of the mammary gland.[2]
- ER-α, the first receptor subtype to be identified in the breast, stimulates cell proliferation in breast cancer by targeting the expression of signaling components of the insulin-like growth factor system.[2]
- PR, an important biomarker of prognosis (especially in HR+ breast cancer), modulates the function of ER-α in breast cancer.[3]

Human Epidermal Growth Factor Receptor 2 (HER2):

- The *HER2* gene, commonly overexpressed or amplified in breast cancer, encodes the receptor tyrosine kinase HER2.[4]
- HER2 upregulation contributes to tumor progression.[4]
- HER2 signaling activation is responsible for increases in proliferation and survival of the primary tumor.[4]
- The signaling activation also promotes cell motility, thus, causing the dissemination of metastatic cells.[4]



AI=Aromatase Inhibitor; E2=Estradiol; EGF=Epidermal Growth Factor; EGFR=Epidermal Growth Factor Receptor; ER=Estrogen Receptor; ERK=Extracellular Signal-Regulated Kinase; ER2=Human Epidermal Growth Factor Receptor mAb=Monoclonal Antibody; MEK=Mitogen-Activated Protein Kinase; mTOR=Mammalian Target of Rapamycin; PI3K=Phosphoinositide 3-Kinase; PR=Progesterone Receptor; RAS=Rat Sarcoma; SERD=Selective Estrogen receptor Degrader; SERM=Selective Estrogen Receptor Modulator; TKI=Tyrosine Kinase Inhibitor.

Image is derived from Ref. 1 and 5. 1. Prat A, Baselga J. *Nat Clin Pract Oncol*. 2008;5(9):531-42. 2. Gross JM, Yee D. *Breast Cancer Res*. 2002;4(2):62-64. 3. Li Z, et al. *Drug Des Dev Ther*. 2022;16:305-314. 4. Freudenberg JA, et al. *Exp Mol Pathol*. 2009;87(1):1-11. 5. Lloyd MR, et al. *Ther Adv Med Oncol*. 2022,14:1–25.

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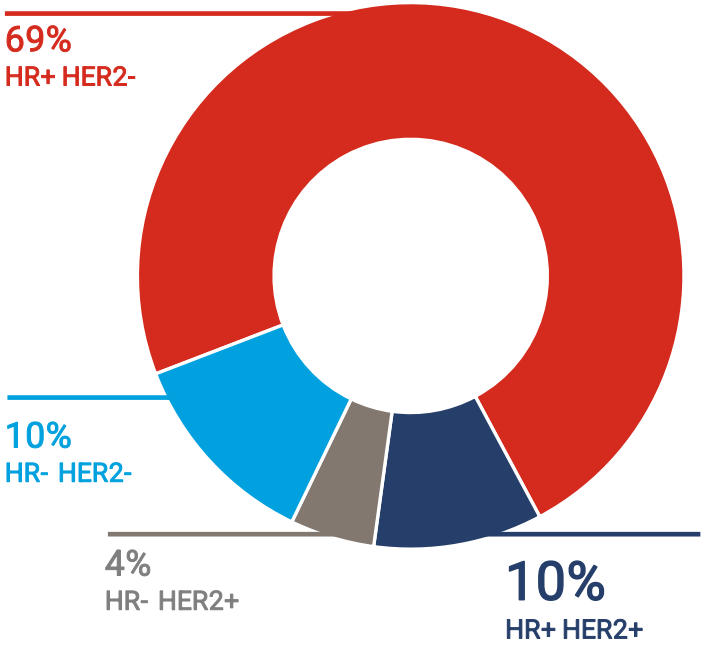
Breast Cancer: Subtypes

- Breast cancer is typically grouped into 4 subtypes based on the status of hormonal biomarkers and presence or absence of HER2 overexpression.[1,^]

BREAST CANCER CATEGORIES[1,2,#,*]



HR+, HER2-	ER+ and/or PR+	No HER2 amplification[1] (HER2-)
HR+, HER2+	ER+ and/or PR+	With HER2 amplification[1] (HER2+)
HR-, HER2+	ER-/PR-	With HER2 amplification[1] (HER2+)
HR-, HER2- (TNBC)	ER-/PR-	No HER2 amplification[1] (HER2-)

[^]HER2+ tumors are defined either as IHC(3+) or IHC(2+)/FISH+.[2] [#]Incidence among US patients based on SEER 2016-2020 data. *Note: The total will not add up to 100% since unknown tumors make up 7% of the total female breast cancer cases. ER=Estrogen Receptor; FISH=Fluorescence *in situ* Hybridization; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; IHC=Immunohistochemistry; PR=Progesterone Receptor; SEER=Surveillance, Epidemiology, and End Results; TNBC=Triple-Negative Breast Cancer.

1. https://seer.cancer.gov/statfacts/html/breast-subtypes.html (Accessed Oct. 27, 2023). 2. Horimoto Y, et al. *BMC Cancer*. 2022;22(1):242.

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Breast Cancer: Stages

- Metastatic breast cancer can occur *de novo* (28%) or recur after the treatment of early-stage or locally advanced breast cancer (72%)[1]

	Stage[2-3]	Definition	5-year survival[3-5]
Early stage (Not spread beyond breast tissue and nearby lymph nodes)	0	Noninvasive; carcinoma in situ	86-99%
	I	Tumor size <2 cm	
	IIA IIB	Tumor size <5 cm without spreading or up to 2 cm with spread to 1-3 lymph nodes Tumor size >5 cm without spreading or 2-5 cm with spread to 1-3 lymph nodes	
	IIIA	Any size tumor without spread to the chest wall/skin with spread to 4-9 nearby lymph nodes; tumor >5 cm and spread to 1-3 nearby lymph nodes	
Locally advanced (Progressed locally, but not yet spread to distant tissues)	IIIB IIIC	Disease spread to chest wall or skin of breast and <9 axillary lymph nodes Disease spread to ≥10 axillary lymph nodes or lymph nodes in the collarbone or breastbone	
Metastatic Breast Cancer	**IV**	**Disease spread to distant organs**	**28%**

1. Mariotto AB, et al. *Cancer Epidemiol Biomarkers Prev.* 2017;26(6):809-815. 2. Giuliano AE, et al. *AJCC Cancer Staging Manual.* 2017.
3. https://www.breastcancer.org/symptoms/diagnosis/staging (Accessed Oct. 27, 2023). 4. Stages Archives - National Breast Cancer Foundation (Accessed Oct. 27, 2023). 5. https://www.webmd.com/breast-cancer/breast-cancer-survival-rates (Accessed October 27, 2023).

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Metastatic Breast Cancer: Introduction

~ THIRTY PERCENT

of patients diagnosed with early breast cancer will later develop recurrent and/or metastatic disease.[1]

It is estimated that
~297,790
WOMEN
in the US are living with
METASTATIC BREAST CANCER[2-4]

MEDIAN SURVIVAL
after
METASTATIC BREAST CANCER
diagnosis is
~2 YEARS[5]

- Incidence of *de novo* cases of MBC
  - 3-6% of new breast cancer diagnoses in high-income countries, including US[5]
- MBC is incurable and therapeutic goals are mostly palliative[6,7]

MBC=Metastatic Breast Cancer.

1. Nelson DR, et al. *PLoS ONE.* 2022;17(2): e0264637. 2. 2023-Breast-Cancer-Facts-Figures-FINAL.pdf (stopbreastcancer.org) (Accessed Oct. 27, 2023). 3. Mariotto AB, et al. *Cancer Epidemiol Biomarkers Prev.* 2017;26(6):809-815. 4. Mayer M, Grober S. lbbc.org/LBBCsilentvoices. 2006. (Accessed Oct. 27, 2023) 5. Daily K, et al. *Clin Breast Cancer.* 2021;21(4):302-308. 6. Cardoso F, et al. *Ann Oncol.* 2018;29(8):1634-1657. 7. Irvin W Jr, et al. *Oncologist.* 2011;16(9):1203-1214.

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Breast Cancer Classification: Biologic Subtypes

- Biologic subtypes were initially defined by gene expression patterns, but it can also be approximated using IHC assays for ER, PR, HER2, and Ki-67. However, variability in the definitions of the different subtypes has been noted[1-4]
- Variation of breast cancer characterization between studies is mostly because of different intrinsic gene sets used for cluster analysis[3]

Luminal A

ER+ PR+ HER2-

- Most common (50-60%) of all breast cancers[2,3]
- Slow growth and better prognosis[2,3]
- Low Ki-67[1-3]

Luminal B

ER+ PR+ HER2+/HER2-

- 15-20% of all breast cancers[2,3]
- Slightly faster growth and worse prognosis than luminal A[2,3]
- High Ki-67[1-3]

HER2 Enriched

ER- PR- HER2+

- 15-20% of invasive breast cancer[2,3]
- Faster growing than luminal A/B[2]
- Worse prognosis[2,3]

Triple-Negative/Basal-Like

ER- PR- HER2- Basal markers+

- Approximately 15% of invasive breast cancer[2]
- Associated with women having *BRCA1* and *p53* mutations[2]
- Fast growing and worst prognosis[2,3]

BRCA1=Breast Cancer Susceptibility Gene 1; ER=Estrogen Receptor; HER2=Human Epidermal Growth Factor Receptor 2; IHC=Immunohistochemistry; PR=Progesterone Receptor. 1. Feng Y, et al. *Genes Dis.* 2018;5(2):77-106. 2. Eliyatkın N, et al. *J Breast Health*. 2015;11(2):59-66. 3. Yersal O, Barutca S. *World J Clin Oncol.* 2014;5(3):412-424. 4. Erber R, Hartmann A. *Breast Care*. 2020;15:327-336.

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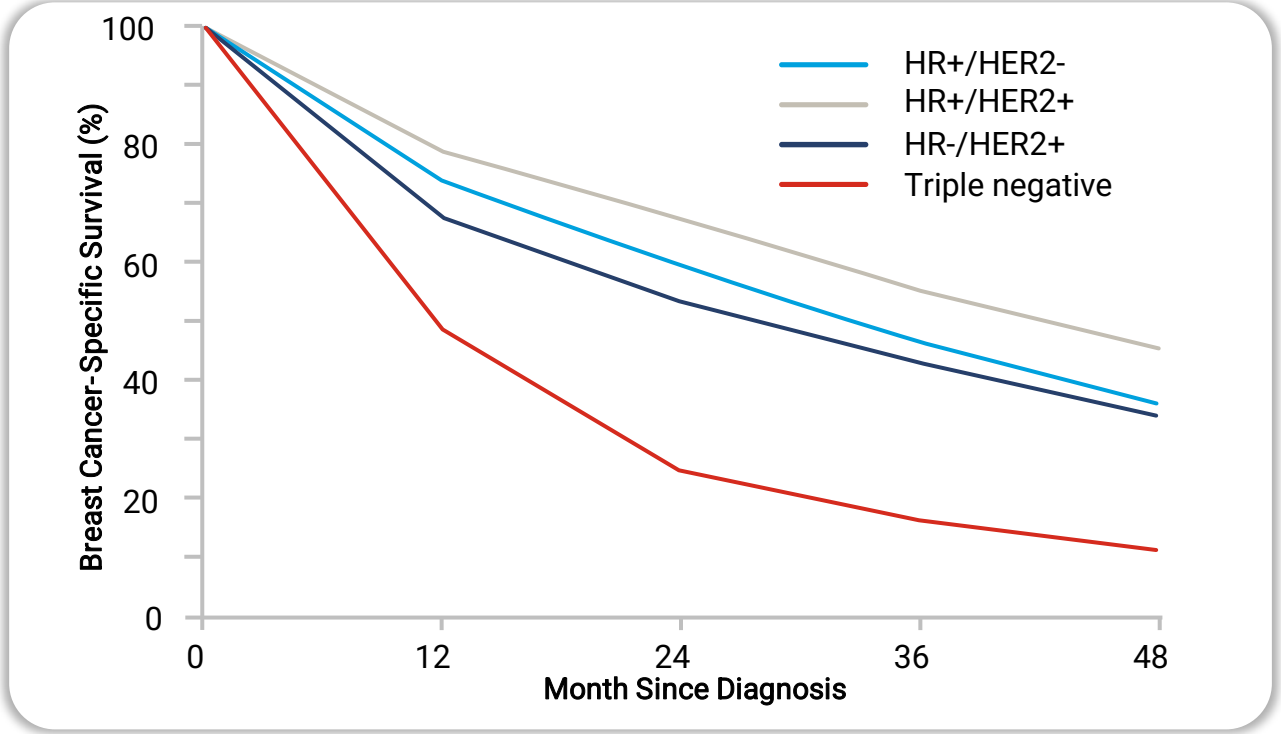
HR+, HER2– Breast Cancer: Heterogeneous Disease With Various Subtypes and Prognoses

Breast Cancer-Specific Survival Curves for Stage IV Disease by Molecular Subtypes[1]



HR+ breast cancer is the most common form of breast cancer. It has distinct subtypes, each with a different prognosis.[2,3]

INDOLENT DISEASE → AGGRESSIVE DISEASE

HR+, HER2- ABC[3,4]

- Asymptomatic
- Luminal A (50% of invasive breast cancer)
- Indolent course
- Bone-only disease
- Long-term survival

HR+, HER2- ABC[3,4]

- Rapid disease progression
- Luminal B (20% of invasive breast cancer)
- Resistance to therapy
- Visceral involvement
- Shorter survival

ABC=Advanced Breast Cancer; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor

1. Howlader N, et al. *Cancer Epidemiol Biomarkers Prev.* 2018;27(6):619-626. 2. Howlader N, et al. *J Natl Cancer Inst.* 2014;106(5):dju055. 3. Eliyatkın N, et al. *J Breast Health.* 2015;11(2):59-66. 4. Yersal O, et al. *World J Clin Oncol.* 2014;5(3):412–424.

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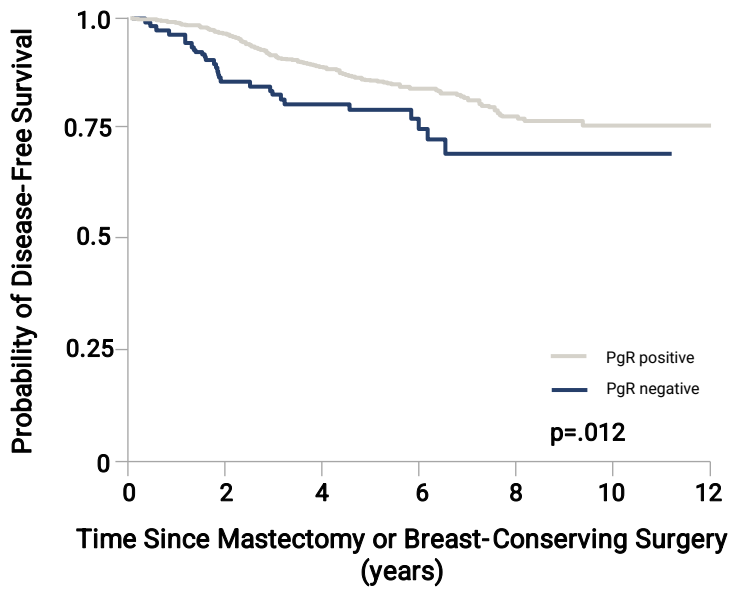
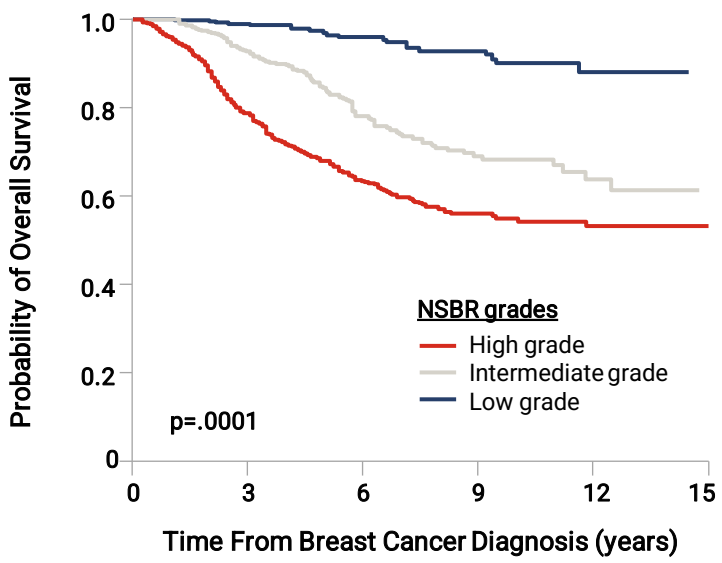
Additional Risk Factors Resulting in a Less-Favorable Prognosis

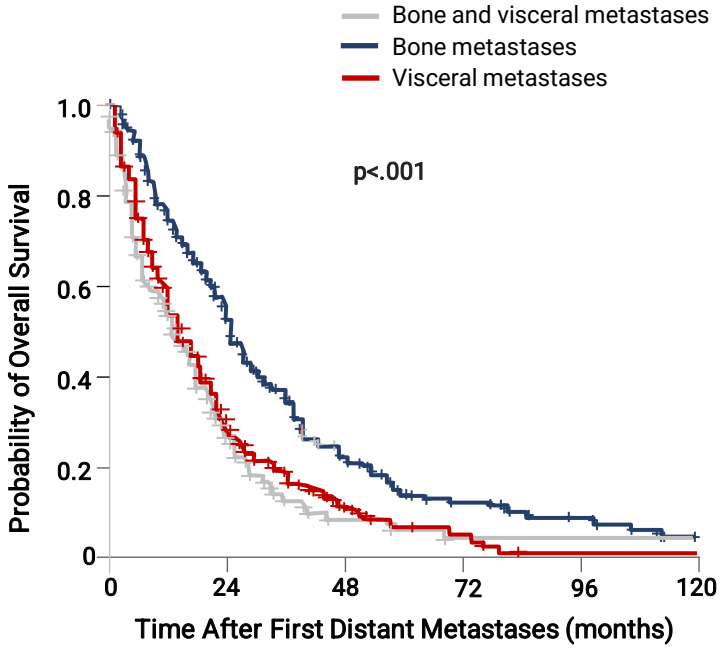
PgR Status[1,a]



Tumor Grade[2]



Site of Metastases[3]



[a]The PR+ subgroup included patients with ER+ (n=972) and ER- (n=219) disease. ER=Estrogen Receptor; NSBR=Nottingham Modification of Scarff-Bloom-Richardson (grading scheme); PgR=Progesterone Receptor.

1. Sun J-Y, et al. *Onco Targets Ther*. 2016;9:1707-1713. 2. Dalton LW, et al. *Mod Pathol*. 2000;13(7):730-735. 3. Solomayer E-F, et al. *Breast Cancer Res Treat*. 2000;59(3):271-278.

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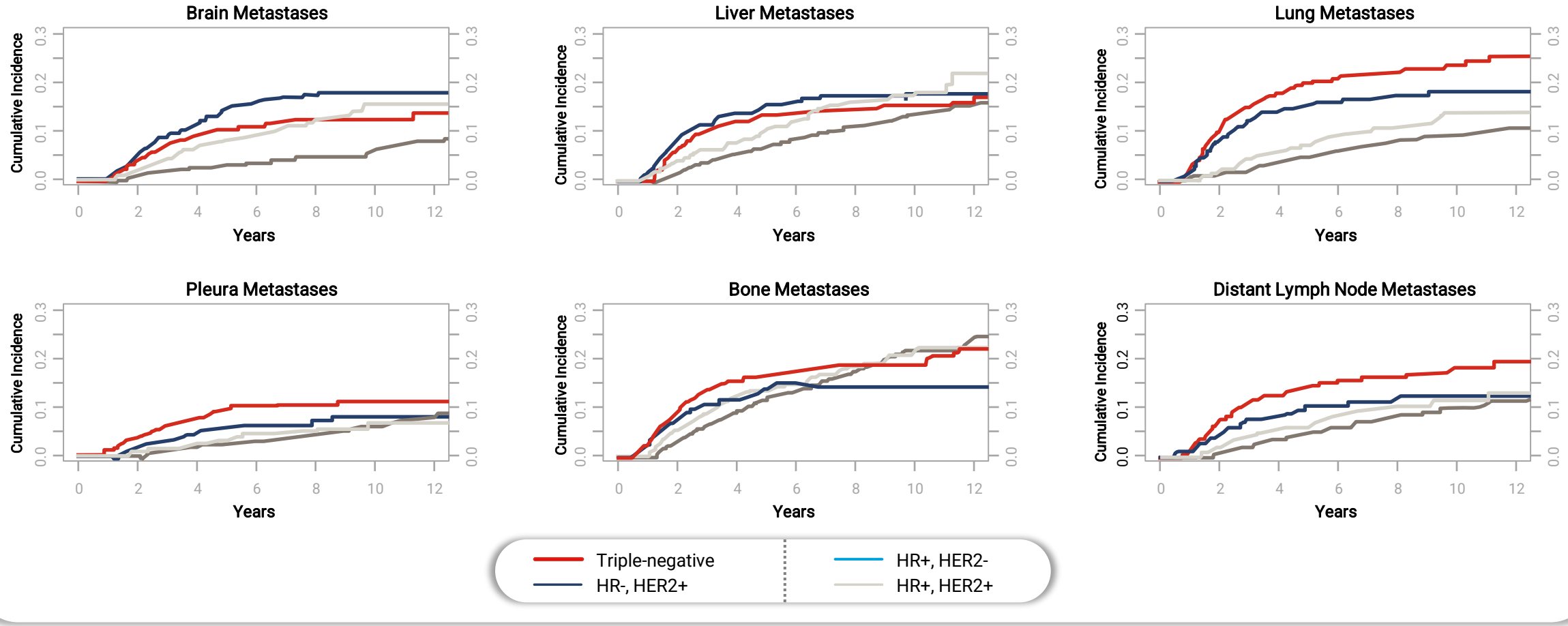
Cumulative Incidence Curves: Estimation by HR, HER2 Status, and Recurrence Site[1]



Cumulative incidence is calculated as the number of new events or cases of disease divided by the total number of individuals in the population at risk for a specific time interval.
HR=Hormone Receptor; HER2=Human Epidermal Growth Factor Receptor

1. Hess KR, Esteva FJ. *Breast Cancer Res Treat.* 2013;137(2):449-455.

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Site of Recurrence by ER Status

Site of Recurrence	ER Status[a]		
	ER+ (%) N=682	ER- (%) N=333	P value
Bone	44	33	.0008
Soft tissue	41	51	.0036
Multiple sites	31	44	.001
Lung	15	28	.0001
Contralateral breast	12	6	.0071
Liver	10	17	.0007
Other viscera	9	9	.98
Brain	5	9	.0025

Note: *P*-values from chi-square test. [a]Data from patients who had ER assays performed between 1971-1983. ER=Estrogen Receptor. Clark GM, et al. *J Clin Oncol.* 1987;5(1):55-61.

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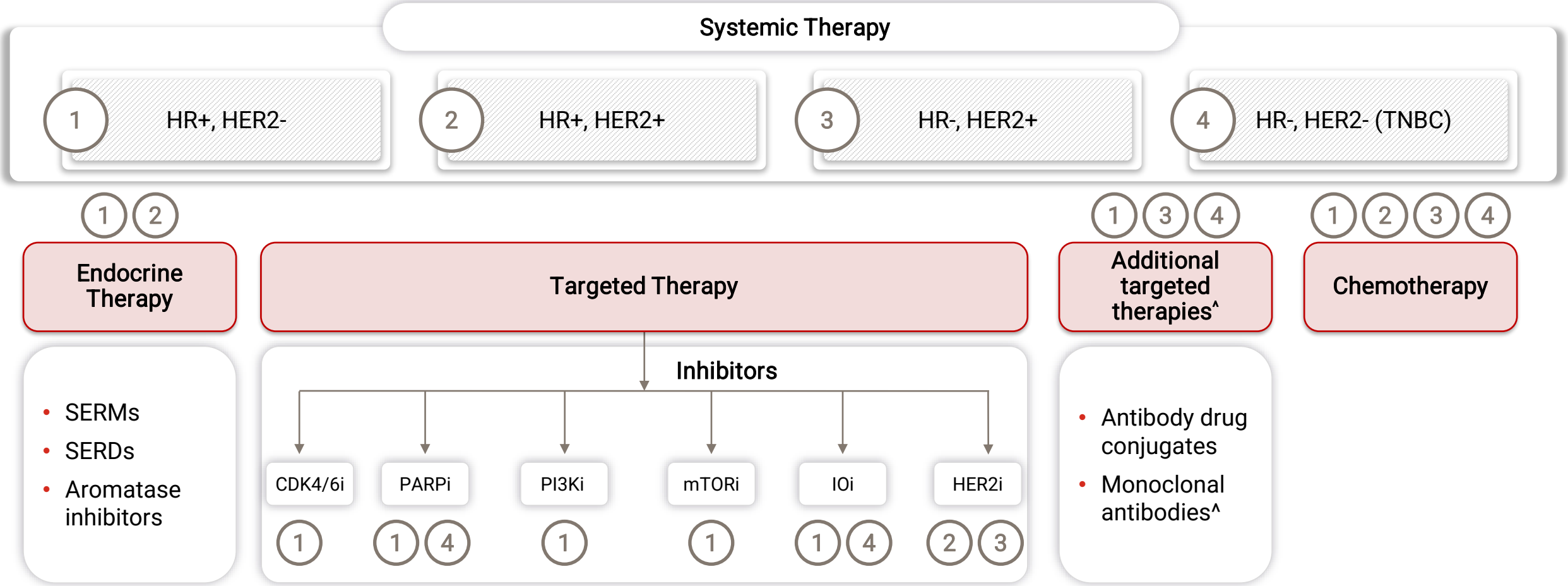
MBC: Systemic Treatments[1,2]



◯ Number marked against each therapy indicates the type of treatment currently used. ^Anti-HER2 therapy. CDKi=Cyclin-Dependent Kinase Inhibitor; HER2i=Human Epidermal Growth Factor Receptor 2 Inhibitor; IOi=Immuno-oncology Checkpoint Inhibitor; mTORi=Mechanistic Target of Rapamycin Inhibitor; PARPi=Poly (ADP-Ribose) Polymerase Inhibitor; PI3Ki=Phosphoinositide 3-Kinase Inhibitor; SERD=Selective Estrogen Receptor Downregulator; SERM=Selective Estrogen Receptor Modulator; TNBC=Triple-Negative Breast Cancer. 1. ESMO mBC Guidelines_2021 (Accessed Oct. 27, 2023); 2. Liedtke C, Kolberg HC. *Breast Care (Basel).* 2016;11(4):275-281.

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MBC: Targeted Therapies

Drug Classes[1]		Mechanism of Action
Targeted therapy for HER2+ breast cancer	Monoclonal antibodies[2,3]	• HER2-targeted humanized mAb, designed to attach to the HER2 protein on cell surface; thus, inhibiting tumor growth
	Antibody-drug conjugates[3,4]	• HER2-targeted mAb linked to a chemotherapy agent, attaches itself to the HER2 protein on tumor cells, bringing the chemo directly to the tumor cells.
	Kinase inhibitors[5]	• Suppress tumor growth
Targeted therapy for HR+ breast cancer	CDK4/6 inhibitors[6]	• Induce cell cycle arrest, leading to reduced cell proliferation.
	Antibody-drug conjugates[1]	• An antibody-drug conjugate (ADC) is a monoclonal antibody joined to a chemotherapy drug. The antibody acts like a homing signal by attaching to a specific protein on cancer cells, bringing the chemo directly to them.
	mTOR inhibitors[5,7]	• Reduce cell proliferation (growth), decrease angiogenesis (development of new blood vessels), and promote cell death
	PI3K inhibitors[7]	• Induce cell death in PIK3CA-mutated breast cancer cells
Targeted therapy for women with *BRCA* gene mutations	PARP inhibitors[8,9]	• Induce cytotoxicity, DNA damage, and cancer cell death • Decrease cell proliferation
Targeted therapy for triple-negative breast cancer	Immune checkpoint inhibitors[10]	• May augment T cell antigen-priming and activation and antibody-dependent regulatory T cell cytotoxicity

Abbreviations: CDK=Cyclin-Dependent Kinase; EGFR=Epidermal Growth Factor Receptor; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; mTOR=Mechanistic Target of Rapamycin; PARP=Poly (ADP-Ribose) Polymerase; PI3K=Phosphoinositide 3-Kinase; PIK3CA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; VEGFR=Vascular Endothelial Growth Factor Receptor.

References: 1. https://www.cancer.org/cancer/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html. (Accessed Oct. 27, 2023); 2. Bernard-Marty C, et al. *Drugs.* 2006;66(12):1577-1591; 3. Ferraro E, et al. *Breast Cancer Res.* 2021;23(1):84; 4. Corti C, et al. *Cancers (Basel).* 2021;13(12):2898; 5. Wujcik D. *Semin Oncol Nurs.* 2014;30(3):139-146; 6. Elfgen C, Bjelic-Radisic V. *Cancers (Basel).* 2021;13(23):5994; 7. Brachmann S, et al. *Curr Opin Cell Biol.* 2009;21(2):194-198; 8. Cortesi L, et al. *Target Oncol.* 2021;16(3):255-282; 9. Shi Y, et al. 2014; *Chin J Cancer Res.* 26(2):142–147. 10. Farshbafnadi M, et al. *Int Immunopharmacol.* 2021;98:107876.

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Summary

- It is estimated that ~297,790 women in the United States are living with metastatic breast cancer
- Breast cancer is classified on the basis of histology, protein expression, and molecular subtypes.
  - Ductal and lobular carcinoma
  - HR and HER2 status
  - Luminal A, luminal B, HER2-enriched, and triple negative/basal-like
- Various factors are associated with poor prognosis of metastatic breast cancer.
  - PR-, high tumor grade, and visceral metastases
- Current treatment paradigms include:
  - Endocrine therapy (HR+ breast cancer)
  - HER2 therapies (HER2+ breast cancer)
  - Other targeted therapies (HR+/HR- and TNBC)
  - Chemotherapy

HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; PR=Progesterone Receptor.

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