Breast Cancer Basics

- Pathology
- Screening guidelines
- Risk factors

→ Pathology of invasive Breast cancer:

WHO classification:

- Invasive ductal carcinoma No special type (NST) — 70-80%
- Other special types → invasive lobular carcinoma
  - Tubular
  - mucinous
  - medullary
  - papillary
  - cribriform

  } favourable outcome

  micropapillary CA → higher risk of lymphovascular invasion.
- Sarcomas
- adenoid cystic
- Secretory CA

* Nottingham grading / modified Bloom & Richardson grading

Criteria	Score	Description
Gland formation	1	(1): >75% of tumour forms gland
	2	(2): 10%–75% tumours formation
	3	(3): <10% forms gland
Mitosis count	1	(1): <11 mitosis in 10 HPF
	2	(2): 11–20 mitosis in 10 HPF
	3	(3): >20 mitosis in 20 HPF
Nuclear atypia	1	(1): Small general, even cores
	2	(2): Average increment in size
	3	(3): Fluctuation marked variety

Total score = 3 to 5 = well differentiated / Grade 1
6 & 7 = moderately diff / Grade 2
8 & 9 = Poorly diff / Grade 3

* Prognostic factors in breast cancer

- Axillary LN involvement
- Histologic grade
- Biomarker expression – ER / PR / HER2 neu
- Patient age – <35 yrs is poor prognosis
- Lymphovascular space invasion

Ki 67 → to differentiate luminal A from B.
→ high inter lab variability.

* Tumor Biomarkers in breast cancer:

– Hormone Receptors – ER & PR

Proportion Score	
Score	*Percentage of stained cells*
0	No cells are ER positive
1	≤1% cells are ER positive
2	1-10% cells are ER positive
3	11-33% cells are ER positive
4	34-66% cells are ER positive
5	67-100% cells are ER positive
Intensity Score	
Score	*Intensity of staining*
0	Negative
1	Weak
2	Intermediate
3	Strong
Allred Score (Allred score=Proportion Score + Intensity Score)	

N	Allred score	Final result
1	0/8	Negative
2	1/8 – 2/8	Negative
3	3/8 – 4/8	+ ve Weak
4	5/8 – 6 /8	+ ve Moderate
5	7/8 – 8/8	+ ve Strong

* according to ASCO:
< 1% staining → negative
1 – 10% staining → Low positive
Limited data on benefit of endocrine therapy
> 10 % staining → ER positive.

→ If ER –ve, PR +ve :
- Data regarding benefit of endocrine therapy limited.

→ HER 2 testing :

Testing by IHC

Score to Report	HER2 Overexpression	Assessment of Protein Staining Pattern
0	Negative	No staining is observed, or membrane staining in fewer than 10% of tumor cells.
1+	Negative	A faint or barely perceptible membrane staining is detected in more than 10% of tumor cells. The cells are only stained in part of the membrane
2+	Borderline	A weak to moderate complete membrane staining is observed in more than 30% of tumor cells.
3+	Positive	A strong complete membrane staining is observed in more than 30% of the tumor cells.

HER2: Human epidermal growth factor receptor 2

→ Further testing by FISH

HER2 testing by validated dual probe ISH assay
- positive if copy number > 6 (or)
HER2/CEP17 Ratio >/ 2

HER2 low → IHC 1+ and IHC 2+ / FISH negative
- Benefit from TDxd

HER2 Ultra low → IHC 0
Benefit from TDxd
(DESTINY-Breast trial)

TABLE 53.5

Association of Clinicopathologic Features of Breast Cancer with Intrinsic Subtype

Intrinsic Subtype	Luminal A	Luminal B	*HER2* Enriched	Basal-Like
ER/PR expression	Positive—strong	Positive—variable	Positive or negative	Negative
HER2 amplification	Rare	Rare though small percentage positive	Common	Negative
Grade	Low to intermediate	Intermediate to high	Intermediate to high	High
P53 mutation	Rare	Uncommon	Common	Common
Ki67	Low	Intermediate to high	High	High
DNA copy number	Diploid	Aneuploid	Aneuploid; high genomic instability	Aneuploid; high genomic instability
mRNA expression signature	High ER cluster, low proliferation	Lower ER cluster, high proliferation	High *HER2* amplicon, high proliferation	Basal signature, high proliferation
10yr LR after BCT	8.1.	10.1.	21.1.	14 .1.
10yr LR after mastectomy	8.1.	14 .1.	17 .1.	19 .1.

molecular subtype is most significant determinant of likelihood of local recurrence.

12WBC

→ Proliferation markers in breast cancer:

- S-phase fraction
- cellular expression of Ki67
- MIB-1
- mitotic index

→ Prognostic indicators in early breast cancer.

- interobserver variability
- lack of uniform thresholds.

→ Apoptosis markers in breast cancer:

- circulating FasL
- Granzyme B
- cytochrome c

→ increase following response to chemotherapy.
→ useful in monitoring response to treatment.

Screening guidelines

→ Breast cancer risk assessment models:

1) Gail model

Risk assessment to be done < 25 years of age

- Age at menarche
- Age at 1st live birth.
- No. of previous breast Bx
- Presence of atypical hyperplasia.
- No. of first degree female relative with breast cancer.

* Used in NSABP - Breast cancer prevention trial
* Under estimates the risk because
  * Does not include 2nd degree relatives
  * Does not include ovarian cancer history.

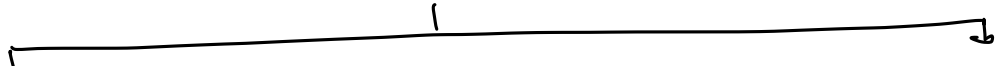
2) Clause model

- Includes 1st and 2nd degree relatives history.

3) BRCAPRO } include strong family history.
4) BOADICEA }

5) Tyrer - Cuzik (IBIS) model
(International Breast Intervention Study)
Cancer

- most accurate
- Includes HLO benign breast histologies. along i family history.



Lifetime risk
< 20%
(Average risk)

- monthly SBE
- Annual CBE
- Annual mammo } after 40yrs age
- Breast awareness

Lifetime risk
> 20%.

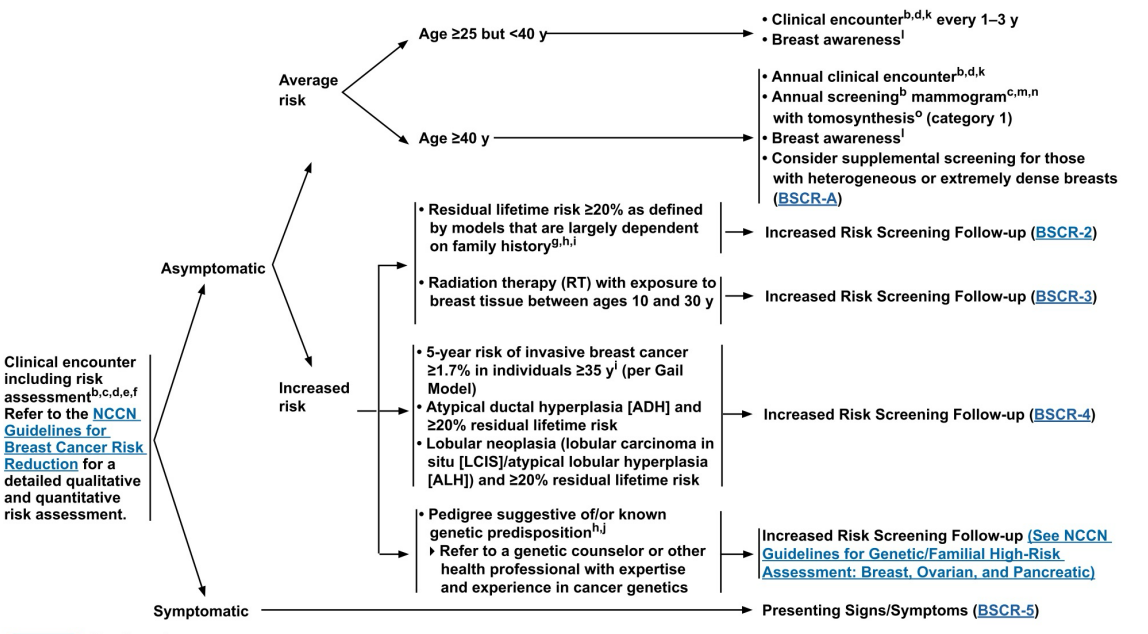
- monthly SBE
- CBE 6-12 mo
- Annual mammo
- Annual MRI

TABLE 53.3

American Cancer Society Guidelines for Magnetic Resonance Imaging Screening

- Annual MRI recommended based on evidence
  - *BRCA* mutation
  - Untested first-degree relative of *BRCA* carrier
  - Lifetime risk of breast cancer 20%–25% or greater, as defined by models that are largely based on family history
- Annual MRI recommended based on expert opinion
  - Radiation to chest between ages 10 and 30 y
  - Li-Fraumeni syndrome and first-degree relatives
  - Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
- Insufficient evidence to recommend for or against MRI
  - Lifetime breast cancer risk of 15%–20% as defined by models
  - Lobular carcinoma in situ
  - Atypical hyperplasia (lobular or ductal)
  - Extremely or heterogeneously dense breasts on mammogram
  - Personal history of breast cancer, including ductal carcinoma in situ
- Recommend against MRI screening (based on expert consensus opinion)
  - Women at <15% lifetime risk

MRI, magnetic resonance imaging.



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Breast Cancer Screening and Diagnosis
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SCREENING OR SYMPTOM CATEGORY[a]

Increased Risk:

Residual lifetime risk ≥20% as defined by models that are largely dependent on family history[g,h,i]

SCREENING/FOLLOW-UP

- Clinical encounter[b,d,k] every 6–12 mo
  - To begin when identified as being at increased risk
  - Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done
  - Consider referral to a breast specialist as appropriate
- Annual screening[b] mammogram[c,m] with tomosynthesis[o]
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, or after risk assessment if determined to be at high risk, not prior to age 30 y,[p] or begin at age 40 y (whichever comes first)
- Annual breast MRI[q,r] with and without contrast
  - Consider contrast-enhanced mammography (CEM)[b] or molecular breast imaging (MBI)[b] for those who qualify for but cannot undergo MRI. Whole breast ultrasound[b] may be done if contrast-enhanced imaging or functional imaging is not available/accessible
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 y,[s] or after risk assessment if determined to be at high risk, or begin at age 40 y (whichever comes first)
- Consider risk reduction strategies (see NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

→ Risk factors

① Hormonal factors – Relative Risk < 2

* Early menarche - ≤ 9 years (N = 9-15)
  (Each year delay in menarche increases risk by 20%)
* Age at first full term pregnancy < 30 years.
* Duration of exclusive breast feeding - 18-24 months reduces risk by 40%.
* Late menopause. (N = 42-58 years)

Menopause definition

- Spontaneous / induced permanent cessation of menses for ≥ 12 months with Post menopausal levels of serum

Estradiol - 0-30 pg/mL.

FSH - 25 - 150 mIU/mL.

Menopausal status cannot be determined in those receiving ovarian function suppression.

- Abortion (spontaneous / induced) does not increase risk

- HRT – Combined pills increase risk by 25%.
  (women's health Initiative Study)
  ↓
  more likely to have nodal disease & mets compared to placebo group.

- OCP risk →

② Dietary & lifestyle factors – RR < 2

- Alcohol
- ↓ed vit C, folate, & Carotene intake.
- Post menopausal obesity BMI ≥ 31

③ Benign Breast disease RR - 2-4

- Dupont and Page classification of Benign Breast disease and risk of invasive Breast carcinoma.

Lesion Type	Lesion Subtype*	Aggregate Relative Risk of Future Breast Cancer (95% CI)
Nonproliferative	Simple cysts Mild hyperplasia (usual type) Papillary apocrine change	1.17 (0.94–1.47)†
Proliferative without atypia	Fibroadenoma Giant fibroadenoma Intraductal papilloma Moderate/florid hyperplasia (usual type) Sclerosing adenosis Radial scar	1.76 (1.58–1.95)†
Atypical hyperplasia	Atypical ductal hyperplasia Atypical lobular hyperplasia	3.93 (3.24–4.76)†
Lobular carcinoma in situ		6.9–11‡

④ Environmental factors

- Radiation exposure < 30 years age
- mantle cell radiation in Hodgkin's lymphoma