BREAST CANCER

INTRODUCTION

Breast cancer is the second most common cancer among women, following skin cancer. Early detection through mammography significantly improves outcomes by identifying tumors before they metastasize.

Anatomy of the Female Breast

1. The breast is composed of both external and internal structures. Externally, it includes the nipple and areola. Internally, each breast contains 15–20 lobes, which are subdivided into lobules that end in milk-producing bulbs. These structures are connected by ducts that transport milk to the nipple.
2. The breast also contains blood vessels and lymphatic vessels. Lymph, a clear fluid, is transported through lymph vessels to nearby lymph nodes—small, bean-shaped structures involved in filtering harmful substances and supporting immune defense. Key lymph node clusters are located in the axilla (underarm), above the collarbone, and within the chest.

Risk Factors for Breast Cancer

- Advancing age
- Personal history of breast cancer or benign breast disease
- Inherited mutations (e.g., BRCA1/BRCA2)
- Dense breast tissue
- Hormonal and reproductive history, including early menstruation, late menopause, and fewer pregnancies
- Hormone replacement therapy (HRT) during menopause
- Previous radiation to the chest
- Obesity, especially postmenopausal
- Alcohol consumption
- Understanding these anatomical structures and risk factors is critical for early detection, prevention, and management of breast cancer [1].

INCIDENCE,MORTALITY AND PREVALENCE

Category	Both Sexes	Females	Males
New Cases	2,261,419	2,251,719	9,700
Deaths	684,996	679,510	5,486
5-Year Prevalence	8,797,000	8,760,000	37,000

SOURCE [2]

DIAGNOSIS

Breast Cancer Diagnosis Methods

Diagnosis involves clinical examinations, imaging tests, and biopsy procedures.

Clinical Examination:

- **Breast Examination**: Assess for lumps or abnormalities.

Imaging Tests:

- **Mammography**: Low-dose X-ray, cost-effective for screening.
- **Ultrasound**: Sound waves create images, real-time and cost-effective.
- **MRI**: Magnetic field and radio waves for detailed images.
- **PET-CT:** Combines metabolic and anatomical imaging.
- **BSGI**: Nuclear medicine test using radiotracers for imaging.

Biopsy Procedures:

- **FNAC:** Thin needle withdraws cells for quick analysis.
- **CNB:** Larger needle extracts tissue core for comprehensive samples.
- **SLNB:** Determines cancer spread to lymph nodes, guides treatment [3].

BIOMARKER

Biomarkers play a key role in diagnosing and prognosticating breast cancer. Estrogen Receptor (ER) and Progesterone Receptor (PR) positivity predict hormone receptor-positive breast cancer and a better prognosis. Ki-67 (Proliferation Index) helps assess tumor proliferation and guides chemotherapy decisions, especially in Luminal B subtype. CA 15-3 and CA 27-29 are used for monitoring treatment response and disease progression in metastatic breast cancer, though not diagnostic alone. Carcinoembryonic Antigen (CEA) may indicate tumor activity or metastasis. Bcl-2 expression correlates with tumor subtype and prognosis, while p53 mutations are linked to aggressive tumors and poor prognosis [4-9].

CYTOGENETICS

Cytogenetics provides crucial insights into genetic alterations associated with breast cancer, focusing on chromosomal changes linked to tumor development and progression.

Key Chromosomal Abnormalities:

- **Aneuploidy**: Many breast cancer cell lines exhibit abnormal chromosome numbers, ranging from diploid to highly aneuploid forms.
- **Translocations:** Common translocations include 8;11, 8;17, 1;4, and 1;10. Over 98% of these are unbalanced, contributing to tumorigenesis.
- **Deletions and Duplications**: Notable deletions on chromosomes 1, 6, and 7, with duplications observed on chromosomes 18 and 12. The der(1;16) translocation, linked to gains on chromosome 1q, is frequently seen in breast carcinomas [10-11].

PHARMACOGENOMICS

Pharmacogenomics plays a crucial role in tailoring liver cancer treatments based on genetic factors. For Tamoxifen Response, SNPs in ZNF423 and CTSO (rs9940645, rs6810983) predict the benefit of SERM therapy, reducing breast cancer risk in prevention and early-stage cases. Aromatase Inhibitor Metabolism is influenced by CYP19A1 mutations (rs6493497, rs7176005), affecting the efficacy of drugs like Anastrozole and Letrozole in postmenopausal, early-stage patients. Chemotherapy-Induced Neutropenia and Chemotherapy Toxicity are associated with SNPs in genes like HMMR, GSTP1, ABCC4, and CYP3A5, impacting treatment regimens such as 5-FU and Cyclophosphamide. Prognosis and Recurrence in all stages are influenced by TOX3/TNRC9 (rs3803662), with the GG genotype increasing recurrence risk. SERM Sensitivity is impacted by MDM2 SNP309 (rs2279744), influencing response to Tamoxifen and Raloxifene in all stages [12-15].

TREATMENT

Breast cancer treatment is personalized, considering factors like cancer type, stage, and patient health. Chemotherapy uses cytotoxic drugs in adjuvant, neoadjuvant, and palliative settings. Common drugs include anthracyclines (e.g., doxorubicin), taxanes (e.g., paclitaxel), and platinum agents (e.g., carboplatin). Chemotherapy can be delivered intravenously or orally. Radiotherapy utilizes high-energy rays to destroy residual cancer cells post-surgery or in advanced stages. Types include External Beam Radiation Therapy (EBRT), Brachytherapy, and Hypofractionated Radiation Therapy. Hormone Therapy targets hormone receptor-positive breast cancer by blocking or lowering estrogen and progesterone. Key therapies include Tamoxifen, Aromatase Inhibitors, and ovarian suppression. Targeted Therapy focuses on specific cancer cell pathways, such as HER2-targeted therapies (e.g., trastuzumab) and CDK4/6 inhibitors. Immunotherapy enhances immune response, particularly in triple-negative and HER2-positive cancers, with therapies like Pembrolizumab and emerging treatments like CAR-T cell therapy [16].

DRUGS

1. Anastrozole (Aromatase Inhibitor)
    - Dosage: 1 mg daily
    - Indication: HR+ breast cancer
    - Side Effects: Hot flashes, bone loss
    - Alternatives: Letrozole, Exemestane
2. Tamoxifen (SERM)
    - Dosage: 20 mg daily
    - Indication: HR+ breast cancer
    - Side Effects: Hot flashes, blood clots
    - Alternatives: Raloxifene, Toremifene
3. Abemaciclib (CDK4/6 Inhibitor)
    - Dosage: 150-200 mg twice daily
    - Indication: HR+, HER2- advanced breast cancer
    - Side Effects: Diarrhea, neutropenia
    - Alternatives: Palbociclib, Ribociclib

4. Trastuzumab (HER2-targeted monoclonal antibody)
    - Dosage: 4 mg/kg IV weekly
    - Indication: HER2+ breast cancer
    - Side Effects: Cardiotoxicity, infusion reactions
    - Alternatives: T-DM1

5. Capecitabine (Chemotherapy)
    - Dosage: 1250 mg/m^2 twice daily
    - Indication: Advanced breast cancer
    - Side Effects: Diarrhea, hand-foot syndrome
    - Alternatives: 5-FU [17-22]

NUTRIGENOMICS

DNA Methylation & Repair

- Genes: BRCA1, BRCA2
- Compounds: Folate, Fiber, Selenium (e.g., Foxtail, Proso, Sorghum)
- Molecular Function: DNA repair, one-carbon metabolism
- Significance: High intake of fiber, folate, selenium correlates with reduced BRCA1 methylation and lower BC risk.

Phytoestrogen Activity

- Genes: BRCA1, BRCA2, ERα/β
- Compounds: Isoflavones (Genistein, Daidzein), Lignans (e.g., Soy, Flaxseed)
- Molecular Function: Estrogen receptor modulation, anti-proliferative, apoptosis induction
- Significance: Soy and flaxseed reduce BC risk, especially in BRCA mutation carriers.

Antioxidant Response

- Genes: Nrf2, NF-κB, Wnt
- Compounds: Polyphenols, Flavonoids (e.g., Green Tea, Kiwi, Broccoli)
- Molecular Function: Antioxidant, anti-inflammatory, apoptosis modulation
- Significance: Polyphenols reduce metastasis, angiogenesis, and BC cell proliferation.

Omega-3 Fatty Acids

- Genes: FASN, Inflammatory genes
- Compounds: EPA, DHA, ALA (e.g., Indian Mackerel, Flaxseed)
- Molecular Function: Antioxidant, DNA protection
- Significance: Omega-3 supports detoxification, lowers DNA damage.

Estrogen Metabolism

- Genes: CYP1A1, CYP1B1, COMT
- Compounds: Indole-3-carbinol, Sulforaphane (e.g., Broccoli)
- Molecular Function: Estrogen detoxification
- Significance: Cruciferous vegetables reduce hormone-driven BC risk.

Glycoalkaloids and Polyphenols

- Genes: p53, BAX, Caspase-3
- Compounds: Solamargine, Solanine (e.g., Black Nightshade)
- Molecular Function: Apoptosis induction, tumor metastasis suppression
- Significance: Enhances chemotherapy cytotoxicity and inhibits cancer cell proliferation [23-30].

GENES

- HER2:

Type: Oncogene
Function: Tyrosine kinase receptor
Significance: Driver of HER2+ breast cancer; targeted by therapies (e.g., trastuzumab)

- BRCA1:

Type: Tumor Suppressor
Function: DNA repair via homologous recombination
Significance: Mutations increase hereditary breast cancer risk, linked to genomic instability

- RAD51:

Type: DNA Repair Gene
Function: Homologous recombination repair
Significance: Overexpression correlates with poor prognosis

- CCNB1:

Type: Cell Cycle Regulator
Function: G2/M phase transition
Significance: Upregulated in tumors; linked to aggressive subtypes and shorter survival

- CHEK1:

Type: DNA Damage Checkpoint
Function: Cell cycle arrest in response to DNA damage
Significance: High expression linked to chemotherapy resistance and poor outcomes

- CDK1:

Type: Cell Cycle Kinase
Function: Regulation of mitosis and cell division
Significance: Overexpression correlates with higher mortality risk

- **VEGFA:**

Type: Angiogenesis Factor
Function: Vascular endothelial growth factor signaling
Significance: Promotes tumor angiogenesis and metastasis; potential therapy target

- XRCC4:

Type: DNA Repair Gene
Function: Non-homologous end-joining repair
Significance: Elevated expression linked to poor prognosis

- TP53:

Type: Tumor Suppressor
Function: Cell cycle control and apoptosis
Significance: Mutated in ~30% of breast cancers, drives genomic instability

- PTEN:

Type: Tumor Suppressor
Function: PI3K/AKT/mTOR pathway inhibition
Significance: Loss of function linked to therapy resistance and poor prognosis [31-32]

NUTRITIONAL VALUES

Protein:

- Sources: Millets, Soy, Egg, Legumes
- Intake: 46g (women), 56g (men)
- % DV: Men: 13%, Women: 16%

Polyphenols & Lignans:

- Source: Stone Breaker (Phyllanthus niruri)

Fiber:

- Sources: Millets, Flaxseed, Banana Stem
- Intake: 25g (women), 38g (men)
- % DV: Women: 34%, Men: 22%

Iron:

- Sources: Millets, Sardines, Cashew
- Intake: 8mg (men), 18mg (women)
- % DV: Men: 49%, Women: 22%

Calcium:

- Sources: Finger Millet, Sesame, Sardine
- Intake: 1000mg
- % DV: 36%

- Omega-3:
  - Sources: Flaxseed, Sardines
  - Intake: 1.6g (men), 1.1g (women)
  - % DV: >100%

- Zinc:
  - Sources: Millets, Pumpkin Seed, Egg
  - Intake: 11mg (men), 8mg (women)
  - % DV: Men: 28%, Women: 39%

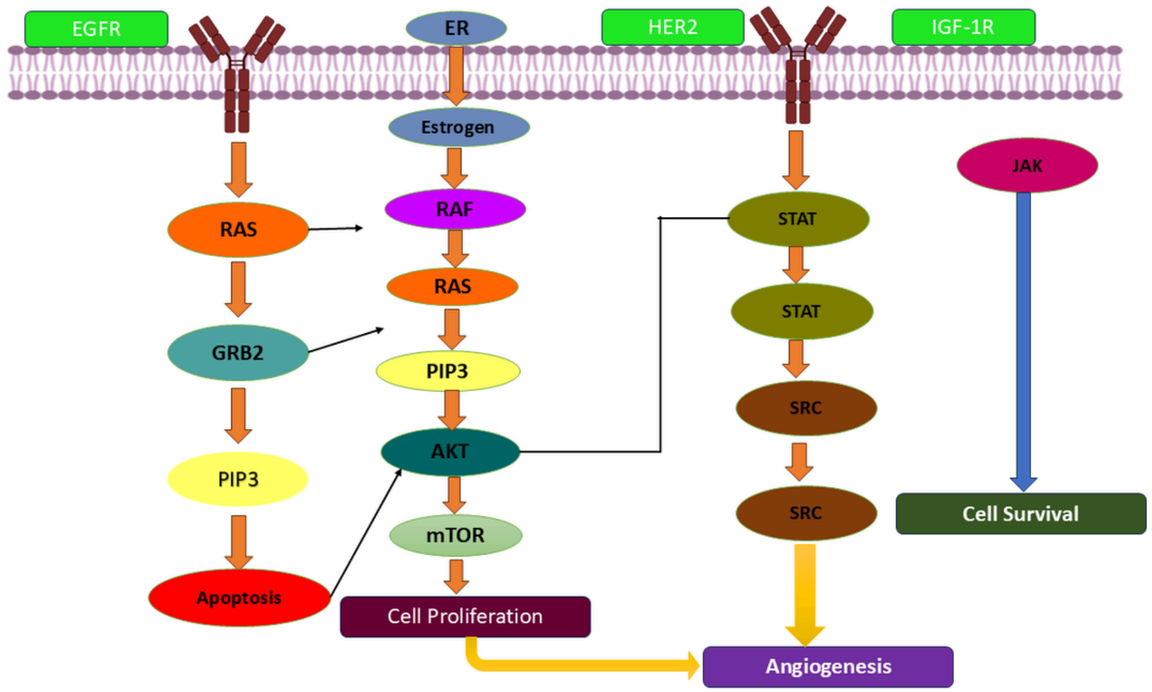
- Vitamin C:
  - Sources: Hibiscus, Watermelon
  - Intake: 90mg (men), 75mg (women)
  - % DV: Men: 40%, Women: 48%

- Antioxidants:
  - Sources: Green Tea, Hibiscus [33-36].

POLYMORPHISM OF BREAST CANCER

Several genetic polymorphisms have been implicated in breast cancer susceptibility and progression. Variants like XRCC1 Arg399Gln and XPD Lys751Gln impair DNA repair mechanisms, elevating cancer risk. hMSH2 Gly322Asp influences tumor grade and lymph node involvement, while XRCC2 Arg188His and promoter SNPs in RAD51 affect homologous recombination efficiency. TIMP-2 polymorphisms (e.g., rs7501477, rs8064344, rs4789936) regulate MMP-2 activity and are associated with tumor invasion and metastasis. BRCA1/BRCA2 variants remain key markers for hereditary breast cancer due to their roles in DNA repair. Emerging evidence highlights non-coding variants like H19 polymorphisms, affecting gene expression via miR-675, and MIR499A rs37746444, which modulates post-transcriptional regulation, as potential contributors to cancer risk, progression, and treatment response [37-41].

SIGNALLING PATHWAYS



Breast cancer progression involves dysregulation of key oncogenic and modulatory signaling pathways. The HER2/ERBB2 pathway, amplified in 15–20% of cases, drives MAPK/ERK and PI3K/AKT activation, promoting proliferation and metastasis. The Estrogen Receptor (ER) pathway regulates genes like CCND1 and MYC, with ESR1 mutations and CDK4/6 crosstalk contributing to therapy resistance. The PI3K/AKT/mTOR axis, frequently altered via PIK3CA mutations or PTEN loss, enhances survival and angiogenesis. Wnt/β-Catenin signaling, activated through CTNNB1 mutations or silencing of inhibitors, supports breast cancer stem cell (BCSC) renewal and EMT. The p53 pathway is inactivated in up to 60% of cases, impairing DNA repair and apoptosis. Modulatory networks such as TGF-β/SMAD shift from tumor-suppressive to pro-metastatic roles, while NF-κB links inflammation to resistance via BCL2 and COX-2. Hedgehog signaling, via SMO/GLI1, maintains stemness and chemoresistance. Lastly, JAK/STAT3, especially in TNBC, promotes immune evasion through MYC stabilization and PD-L1 expression [42-46].

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