**BREAST CANCER LANDSCAPE**

1. ***Breast Cancer Incidence***

 **Global Impact**: Breast cancer accounts for nearly a quarter of all cancers in women globally.

 **Common Diagnosis**: As of 2020, it became the most commonly diagnosed cancer worldwide with 2.3 million new cases.

 **US Statistics (2023)**:

* 297,790 women and 2,800 men diagnosed with invasive breast cancer.
* 55,720 women diagnosed with ductal carcinoma in situ (DCIS).

 **Lifetime Risk**: Increased from 1 in 11 in 1975 to 1 in 8 today.

 **Incidence Rate (2004-2018)**: Rising slightly by 0.5% annually.

 **Median Age at Diagnosis**:

* Overall: 63 years.
* Black women: 61 years.
* White women: 64 years.

 **Military Impact**:

* Active-duty females have a 20% to 40% higher risk.
* Women constitute 17.5% of active-duty personnel in 2022.

 **Young Women (15-39 years)**: Incidence rates increasing by 1.0% annually from 2010 to 2018.

 **Older Women (≥50 years)**:

* Sharp increase in the 1980s.
* Slower increase through 2000, influenced by mammographic screening and hormone-replacement therapy.
* Decline in 2003 linked to reduced use of hormone-replacement therapy after risks were publicized.
* Rates have stabilized since then.

 **Increase in DCIS Incidence**:

* Due to increased breast cancer screening, the incidence of ductal carcinoma in situ (DCIS) has risen dramatically.
* Before 1985, DCIS comprised 2% of breast cancer diagnoses; now it represents nearly one-third of screen-detected cases.

 **Survival and Mortality**:

* DCIS has a near 100% cause-specific survival rate.
* The standardized mortality ratio (SMR) for death from invasive breast cancer post-DCIS diagnosis is slightly above 3.0 over 15 years.
* Younger women (<50 years) diagnosed with DCIS have a higher SMR for breast cancer mortality compared to older women.

 **Challenges with DCIS**:

* It is currently impossible to distinguish which DCIS cases will become invasive.
* Overdiagnosis and overtreatment of DCIS are significant issues.

 **Mammography Screening**:

* Proven to reduce breast cancer-specific mortality in randomized trials.
* Controversy exists over its value and optimal use.

 **Ongoing Research**:

* Trials are evaluating risk-stratified screening programs.
* There is a need for new screening methods to reduce overdiagnosis and overtreatment and to detect cancers earlier to prevent morbidity and mortality.

 **Staging Categories (Figure 2)**:

* Localized, regional, and distant breast cancer
* Metastatic breast cancer rates unchanged since 1975
* Distant-stage disease increased by 2.4% annually (2004-2011)

 **Recent Trends (Figure 3)**:

* Local-stage disease: +0.9% annually
* Regional-stage disease: -0.7% annually
* Distant-stage disease: +2.4% annually (2004-2011), slowing to +0.9% (2015-2019)

 **Key Findings**:

* Metastatic breast cancer rates stable despite mammography
* Slower increase in distant-stage disease in recent years

1. ***Breast Cancer Deaths***

 **Global and U.S. Breast Cancer Deaths:**

* 2020: 684,996 global deaths.
* 2023 (U.S.): 43,170 women and 530 men.
* Median age of death (2016-2020): 70 years.
* 2040 projection: 1.04 million global deaths.

 **Causes of Death:** Metastasis to vital organs (lungs, liver, brain).

 **Mortality Rate Trends:**

* Increase (1975-1990), decline from late 1990s.
* NH Black women: 40% higher mortality rate than NH White women.
* Decline in annual mortality rate:
  + 1.9% (1998-2011)
  + 1.3% (2011-2020)
  + 1.1% (2015-2019)
* 2014-2018 decline:
  + NH Black: 1.4%
  + Hispanic: 1.1%
  + NH White: 0.9%
  + Stable for Asian/Pacific Islander and American Indian/Alaska Native.

 **Factors for Mortality Decline:** Earlier detection, improved treatments.

 **Survival Rates and Recurrence:**

* Five-year survival for localized disease: 99%.
* Recurrence risk varies: 5% to 60%.
* Hormone-positive stage I/II: 10% to 41% metastatic recurrence (5-20 years).

 **Global Incidence and Mortality:**

* Incidence varies by screening in developed countries.
* Mortality rate differences less significant globally.

1. ***Risk Factors***

 **Epidemiologic Studies:** Identify population-level risk factors but not individual predictions.

 **High Risk Factors (>4-fold increase):**

* Age (65+).
* Atypical hyperplasia or lobular carcinoma in situ.
* Pathogenic genetic variations (e.g., BRCA1, BRCA2).

 **Moderate Risk Factors (2- to <4-fold increase):**

* Prior diagnosis of DCIS.
* High postmenopausal hormone levels.
* High-dose chest radiation.
* Dense breasts.
* Two or more first-degree relatives with breast cancer.

 **Mild Risk Factors (up to 2-fold increase):**

* Alcohol consumption, early menarche, high premenopausal hormone levels.
* Late first full-term pregnancy, late menopause, nulliparity.
* No breastfeeding, one first-degree relative with breast cancer.
* Postmenopausal obesity, personal history of ovarian/endometrial cancer.
* Physical inactivity, proliferative breast disease without atypia.
* Long-term menopausal hormone therapy, recent hormonal contraceptive use.
* Adult weight gain, tall height.

 **Attribution of Risk Factors:** Only 41% of U.S. breast cancer cases attributable to key risk factors.

 **Non-modifiable Risk Factors:** Age, family history, reproductive history, ages at menarche/menopause, BRCA status, breast density.

 **Modifiable Risk Factors:** Postmenopausal obesity, combined hormone-replacement therapy, alcohol consumption, smoking, physical inactivity (all weakly to moderately associated).

 **Preventive Medications:** Tamoxifen and raloxifene reduce risk in high-risk women (33% reduction in ER+ breast cancer).

 **Radiation Exposure:** Significant risk factor, especially for young women and BRCA mutation carriers.

 **Molecular Subtype Variations:** Emerging evidence suggests risk factors vary by breast cancer subtype, but more research is needed.

1. ***Breast Cancer Heterogeneity***

 **Molecular Subtypes of Breast Cancer:**

* **Luminal A:** ER+ and/or PR+/HER2-
* **Luminal B:** ER+ and/or PR+/HER2+ or HER2- with high proliferation (Ki67)
* **HER2-overexpressing:** ER-/HER2+
* **Basal-like:** ER-/PR-/HER2- (Triple-negative)

 **Prevalence in the U.S.:**

* 68% ER+ and/or PR+/HER2-
* 10% Triple-negative
* 10% ER+ and/or PR+/HER2+
* 4% ER-/HER2+
* 8% Unknown

 **Variation by Demographics:** Higher triple-negative prevalence in women <50 years (15%) and African American women (23%).

 **Clinical Differences:**

* Targeted therapies available for hormone receptor-positive and HER2-overexpressing tumors.
* Triple-negative disease lacks targeted therapies and has poorer prognosis.

 **Survival Rates:**

* Triple-negative and HER2-overexpressing tumors generally have worse prognoses.
* Prognosis for HER2+ has improved with trastuzumab (Herceptin).

 **HER2 Low-Expressing Breast Cancer:**

* 50% of non-HER2+ cancers have low HER2 protein levels (1+ or 2+).
* Clinical significance is still under study.
* New therapies targeting low HER2 levels, such as trastuzumab deruxtecan-nxki (T-DXd), approved for metastatic HER2-low breast cancer.

1. ***Recurrence and Metastatic Disease***

 **Recurrence and Metastasis:**

* 10-30% of women with invasive breast cancer will experience recurrence and may die from the disease.
* 90% of breast cancer deaths are due to metastatic disease.

 **Current Statistics:**

* 140,230 women in the U.S. were living with metastatic breast cancer as of January 2018.
* 61.4% of these women were initially diagnosed with stages I-III.
* Projected to rise to 169,347 by 2025.

 **Treatment and Survival:**

* Existing treatments (estrogen blockers, radiation, chemotherapy) can shrink or slow metastatic tumors temporarily.
* No cure exists for metastatic breast cancer.
* Median survival with metastatic breast cancer is approximately 3 years.

 **Factors Affecting Survival:** Age at diagnosis, tumor type, whether metastatic disease was diagnosed de novo or is recurrent, and disease-free interval.

 **Risk of Recurrence:**

* Higher in the first 5 years for ER-negative breast cancer.
* Consistent long-term risk for ER-positive tumors, with greater risk after 7 years.
* 75% of breast cancer cases are ER-positive, leading to most breast cancer deaths.

 **Variation by Subtype:** Proportion of node-positive or metastatic stage IV disease at diagnosis varies by breast cancer subtype.

1. ***Breast Cancer Treatments***

 **Historical Treatments:**

* Surgery, radiation therapy, chemotherapy, hormonal therapy.
* Significant changes include less invasive surgery (radical mastectomy to lumpectomy) and fewer lymph node removals.
* Improved quality of life, but no change in mortality statistics.

 **Breast Cancer Subtypes:**

* Defined by ER, PR, and HER2 status.
* Despite heterogeneity, treatments within subtypes are often the same.

 **Targeted Treatments:**

* **ER-positive:** Hormonal therapies (aromatase inhibitors, selective ER modulators), CDK4/6 inhibitors.
* **HER2-overexpressing:** Trastuzumab, antibody-drug conjugates (trastuzumab emtansine, trastuzumab deruxtecan).
* **Triple-negative:** Limited options, immune checkpoint inhibitors (pembrolizumab) combined with chemotherapy, PARP inhibitors for BRCA mutation carriers.

 **Issues with Targeted Therapies:** De novo and acquired resistance.

 **Chemotherapy:**

* Meta-analysis shows reduced recurrence risk, survival benefit mainly for younger women.
* Small improvement in 10-year survival for younger women (7-11%) and for older women (2-3%).

 **Adjuvant Therapies:**

* Small impact on disease-specific survival (5-10%).
* Genomic assays now guide treatment decisions, potentially avoiding unnecessary chemotherapy.

 **Radiation Therapy:**

* Standard with breast-conserving surgery.
* Meta-analysis showed a 5% reduction in 15-year breast cancer mortality.

 **Immunotherapy:**

* Passive immunotherapies (monoclonal antibodies) are standard for some subtypes.
* Active immunotherapies (vaccines, checkpoint inhibitors, adoptive cell therapy) are under research.
* Clinical trials for therapeutic vaccines, oncolytic virus therapies, and combined approaches.

 **Prevention Research:** Two vaccines in Phase 1 trials for high-risk individuals, assessing safety and immunogenicity.

1. ***Cost of Breast Cancer Treatment***

 **Rising Costs of Breast Cancer Treatment:**

* National cost of cancer care in 2015: $183 billion.
* Projected increase to $246 billion by 2030, not including anticipated increases in medical services and prescription drugs.
* Breast cancer accounted for the highest total national costs for medical services and oral prescription drugs in 2015 ($26 billion).

 **Out-of-Pocket Costs:** Breast cancer had the highest out-of-pocket costs for patients in 2019 ($3.14 billion).

 **Financial Toxicity:**

* High financial toxicity for breast cancer patients due to direct and indirect treatment expenses.
* 35% of breast cancer patients in high-income countries and 79% in low- and middle-income countries affected by financial toxicity.

1. ***Morbidity and Mortality Caused by Treatments***

 **Traditional Treatments:**

* **Chemotherapy and HER2-targeted agents:**
  + Risks of morbidity and mortality.
  + Common morbidities include:
    - Cardiac complications.
    - Secondary cancers.
    - Wound infections.
    - Peripheral neuropathy.
    - Lymphedema (most frequent).
    - Reduced shoulder motion.
    - Psychological distress.
* **Radiation Therapy (RT):**
  + Immediate morbidity: Dermal reactions.
  + Long-term consequences: Increased cardiac mortality, new cancers.

 **Newer Treatments:**

* **Targeted agents and immune checkpoint inhibitors:**
  + Less well-characterized toxicities affecting various systems:
    - Hematologic.
    - Endocrine.
    - Pulmonary.
    - Gastrointestinal.
    - Dermatologic.
    - Hepatic.
    - Immune system.
  + Side effects tend to appear early in treatment.
  + Require prompt, multidisciplinary management.
  + Life-threatening toxicities include interstitial lung disease and pneumonitis.

 **Overdiagnosis and Overtreatment:**

* Estimated 31% of all breast cancer cases are overdiagnosed and overtreated.
* Overtreatment can occur through:
  + Overdiagnosis leading to unnecessary treatment.
  + Administration of excessively aggressive therapies.

1. *Drug Development*

 **Cancer Drug Development:**

* In 2020, over 1,300 cancer medicines and vaccines were in clinical testing, with at least 108 specific to breast cancer.
* As of September 2023, the FDA has approved:
  + 83 drugs for breast cancer treatment (chemotherapy, targeted agents, immune checkpoint inhibitors).
  + 4 drugs for breast cancer prevention.
* Between 2010 and 2020, 19 drugs were approved by the FDA for 30 different breast cancer indications, mostly targeted agents.
* Elacestrant (Orserdu), an oral estrogen receptor antagonist, was approved between 2021 and 2023, along with expanded indications for existing drugs.
* Over 2,115 ongoing or recruiting clinical trials are evaluating new drugs, new combinations, or different stages of disease.

 **Impact and Challenges:**

* Despite numerous interventions and trials, the expected impact on mortality has been limited.
* There is uncertainty about whether current drug development and clinical trial approaches can be redesigned to accelerate progress in ending breast cancer.