Ductal Carcinoma
Introduction

Breast Cancer is one of the most common and second largest causes of cancer death in women after lung cancer. Fortunately, the decline in death rate from breast cancer is thought to be due to better early detection and improved treatment. Breast cancer is classified as in situ and invasive based on its location. It is called as in situ when the cancer is still in the lobules and has not spread, or as invasive, when the cells have grown or spread through the duct or lobule and invade through the epithelial basement membrane.

The breast cancer incidence is rising in every country of the world especially in developing countries such as India and Asia. It may be due to - late age at first childbirth, shorter duration of breast-feeding and fewer children. [1]

Incidence & Mortality

Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women. Breast cancer is more than 100 times more common in women than breast cancer in men and more than 13% of the women have the risk of developing breast cancer at any age during her lifetime.

According to recent survey figures shows that, the number of new breast cancer cases is about 115,000 per year in India and the numbers expected to rise to 250,000 new cases per year by 2015 and also the survey found that from year 2020 onwards, the India will add more than 2 million new cancer patients every year. The nation is not yet well prepared to fight against of cancer illnesses in spite of the India adding about a million new cases annually.

Based on cases diagnosed in 2004-2008 from 17 SEER geographic areas the Incidence Rates by Race as follows. [2]

<table>
<thead>
<tr>
<th>Race/Ethnicity[2]</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>124.0 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>127.3 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>119.9 per 100,000 women</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>93.7 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>77.9 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>78.1 per 100,000 women</td>
</tr>
</tbody>
</table>

Genetic Characteristics and Risk Factors[2]:

Risk factors including a family history of breast cancer, prior breast biopsies, nulliparity, and late age of first pregnancy, early menarche, advanced age, and a personal history of breast cancer (in situ or invasive) are similar for both Invasive Breast Cancer (IBC) and Ductal Carcinoma in situ (DCIS).

Increased risk of Breast cancer is due to mutations in the BRCA1 and BRCA2 gene. Of all women with breast cancer, 5% to 10% may have a germ-line mutation of the genes BRCA1 and BRCA2. The estimated lifetime risk of developing breast cancer for women with BRCA1 and BRCA2 mutations is 40% to 85%.
Prognostics Factors\footnote{3}:

Breast cancer is treated by various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. Prognosis of therapy may be influenced by the following clinical and pathological features:

- The stage of the disease
- The age and menopausal status of the patient
- Human epidermal growth factor type 2 receptor (HER2/neu) overexpression
- Proliferative capacity of the tumor (e.g., Ki67).
- The histologic and nuclear grade of the primary tumor.
- The ER and PR status of the tumor.

Types of Ductal Carcinoma

Ductal Carcinoma in Situ (DCIS)\footnote{3}:

Ductal carcinoma in situ is an early, localized cluster of cancer cells that start in the milk passages (ducts) but have not penetrated the duct walls into the surrounding tissue. It is the most common type of noninvasive breast cancer. Ductal carcinoma in situ is also known as "pre-cancerous", "pre-invasive", "non-invasive", or "intraductal carcinoma.

DCIS encompasses a wide range of diseases from low-grade lesions to high-grade lesions that may harbor foci of invasive breast cancer. It comprises a group of histopathologic lesions that have been classified into several subtypes like: micropapillary, papillary, solid, cribriform, and comedo. Comedo-type DCIS consists of cells that appear cytologically malignant, with the presence of high-grade nuclei, pleomorphism, and abundant central luminal necrosis. Comedo-type DCIS appears to be more aggressive, with a higher probability of associated invasive ductal carcinoma.

Invasive Ductal Carcinoma (IDC)\footnote{3}:

IDC is the most common type of breast cancer. It starts in the ducts of the breast but spreads to invade the surrounding normal breast tissue. It is also known as Infiltrating Ductal Carcinoma, Infiltrating Carcinoma. It is usually visualized as a mass with fine spikes radiating from the edges on a mammogram. This lump usually feels much harder or firmer than benign breast lesions such as fibroadenoma on physical examination. The cancerous cells invade and replace the surrounding normal tissues on microscopic examination.

IDC is divided in several histological subtypes like Mucinous, papillary, cribriform, and tubular carcinomas. The prognosis of IDC depends on tumor size, presence of cancer in the lymph nodes, histological grade, presence of cancer in small vessels (vascular invasion), expression of hormone receptors and of oncogenes like HER2/neu.

Diagnosis of Ductal Carcinoma\footnote{3}:

- Mammography is the most effective imaging modality for detecting ductal carcinoma in situ (DCIS).
- Directional vacuum-assisted biopsy (DVAB) is a more accurate diagnostic biopsy technique for women with suspected DCIS.
- High-resolution ultrasound
- Open surgical breast biopsy
- Stereotactic core needle biopsy
Treatment options for Ductal Carcinoma[4]:

- Lumpectomy followed by radiation therapy
- Mastectomy
- Lumpectomy alone
- Hormonal therapy after surgery

Tamoxifen can be used instead of or following radiation treatment after lumpectomy for early-stage cancers that are hormone-receptor-positive. Tamoxifen "pretends" to be estrogen and attaches to the receptors on the breast cancer cells, taking the place of real estrogen. As a result, the cells don't receive the signal to grow. People with hormone-receptor-positive cancer who take tamoxifen can lower their risk of having an invasive cancer or a non-invasive cancer come back.

Aromatase inhibitors such as Anastrozole, Letrozole, and Exemestane are being studied in clinical trials to find out if they are effective in reducing the risk of recurrence in people with DCIS. These medications reduce the amount of estrogen produced in a woman's body after she goes through menopause. The main sources of the hormone for those women are the adrenal glands and fat tissue, not the ovaries.

Recently, it was proposed that Trastuzumab a monoclonal antibody against human epidermal growth factor receptor (HER)-2/neu, could be effective in the treatment of DCIS—both in downstaging disease to permit less extensive surgery and in preventing the transition of DCIS to IBC.

New Developments on Ductal Carcinoma[4]:

- Further research is ongoing to better define the role of adjuvant hormonal therapy in the management of women with ductal carcinoma in Situ (DCIS).
- Research is ongoing to better define the role of radiation therapy in the management of women with DCIS.
- Further research is being done to more accurately identify women with DCIS who are at high risk for recurrence of breast cancer (invasive or in situ).
- Further research is ongoing to better define the role of adjuvant hormonal therapy in the management of women with ductal carcinoma in Situ (DCIS).
- Research is ongoing to better define the role of radiation therapy in the management of women with DCIS.
- Further research is being done to more accurately identify women with DCIS who are at high risk for recurrence of breast cancer (invasive or in situ).
- Newer imaging techniques are being explored to improve the accuracy of early breast cancer screening and detection.
- The role of oral contraceptives as a risk factor for DCIS is being studied.
- Investigation being done on the use of biological markers that can potentially more accurately predict the risk of recurrence in patients with DCIS following surgery is being.
- The risk of recurrence following treatment of DCIS with skin-sparing mastectomy and breast reconstruction is under investigation.
- The prospective role of newer selective estrogen receptor modulators (SERMs) as adjuvant therapy in women with estrogen-receptor positive DCIS is being investigated.
- Cyclo-oxygenase2 (COX-2) inhibitors role in the treatment of DCIS is under investigation.
- Mammary ductoscopy, a new imaging technique is emerging as a potentially important tool in guiding breast-conserving surgery for DCIS.
- Research is ongoing for the development of selective estrogen receptor modulators, or SERMs that have antiestrogenic effects at the level of both breast and uterine tissue while maintaining the beneficial estrogen-like effects on bone mineral density and the cardiovascular system.
Multidrug Resistance in Breast Cancer$^6$:

Resistance to cytotoxic chemotherapy is the main reason for therapeutic failure and death in women suffering from breast carcinoma. Usually, patients refractory to chemotherapeutic treatment regimens show resistance to multiple antineoplastic agents of different structure and mode of action, i.e. the cancerous breast tissue exhibits a multidrug resistance (MDR) phenotype. MDR of breast cancer is multifactorial and heterogeneous. Overexpression of various members of the superfamily of ABC (adenosine triphosphate binding cassette)-transporters have been shown to be associated with MDR in solid tumors including breast cancer. In addition to the classical MDR transporter P-glycoprotein (P-gp) additional ABC-transporters such as MRP1 or BCRP have been analyzed concerning their role in clinical MDR of breast cancer. Besides the “upstream” factors like transcription factors regulating the gene activity of ABC transporter encoding genes, such as the Y-box transcription factor YB-1 were demonstrated to play a role in MDR of mammary carcinoma.

Conclusion:

Breast cancer is the most common and leading cause of cancer deaths among women worldwide. The breast cancer incidence is rising in every country of the world especially in developing countries such as India and Asia. In 2000, breast cancer resulted in an estimated 189,000 deaths in developed countries and 184,000 deaths in developing countries, accounting for 16 and 12 percent, respectively, of all cancer deaths in women. Over the past several decades, the risk of breast cancer in developed countries has increased by one to two percent annually. While data for developing countries are limited, cancer registries suggest that age-standardized incidence rates are rising even more rapidly in low-incidence regions such as Africa and Asia. Researchers believe that lifestyle, socioeconomic, and associated changes in menstrual patterns are responsible for rising risk in developing countries. In addition, increases in life expectancy will cause the burden of breast cancer in developing countries to rise sharply in the years to come, since older women are far more likely than younger women to get the disease. Nearly 220 trials are going on throughout the world on Ductal carcinoma. Neoadjuvant therapy and the use of trastuzumab for DCIS are under investigation and may be future treatment options for DCIS. As a result of these trends, there will be a broad scope for research on Ductal carcinoma in developing countries.

References

1. Boughey JC et al. Current Treatment and Clinical Trial Developments for Ductal Carcinoma In Situ of the Breast.
6. Hermann Lage ; Humboldt University Berlin, Charité Campus Mitte, Institute of Pathology, Schumannstr. 20/21, D-10117 Berlin, Germany.