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Review Article

An Overview of Breast Cancer Epidemiology, Risk Factors, Classification, Genetics, Diagnosis and Treatment

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ABSTRACT

Breast cancer (BC) is the most common form of female cancer worldwide, including India. The incidences of breast cancer cases have shown a drastic increase in our country in the last few decades. They are more prevalent in metro cities like Mumbai, Delhi, Bengaluru, Hyderabad, Bhopal, Kolkata, Chennai and Ahmedabad. It is estimated that one in twenty-eight women in India is likely to develop BC during her lifetime (with 1 in 22 for urban women and 1 in 60 for the rural women). The survival rate for BC is low in India because most of the cases are detected at advanced stages. There are a number of risk factors associated with breast cancer, some are modifiable while others are non-modifiable. The classification is done at the histological level and molecular level. At the molecular level breast cancer is a very heterogeneous disease. BC is curable if detected early, hence early diagnosis plays a key role in survival of the patients. The signs and symptoms of BC can be detected by simple self-examination. With the increased awareness and advancement in diagnostic techniques, like mammography, breast ultrasound and breast MRI, the number of cases detected at early stages are increasing and also the number of false-positive cases are decreasing. Once the diagnosis is confirmed, biopsy is done to assign the Stage, Grade, Biomarkers, Genetic status and Molecular profile of the tumour. The treatment is planned on the basis of tumour type which includes surgery, chemotherapy, radiotherapy, targeted therapy, hormonal therapy and immunotherapy.

Keywords: Breast cancer, risk factors, classification, diagnosis, treatment

1. INTRODUCTION

Breast cancer (BC) is a disease of breast tissues. It's a multifactorial disease, mostly sporadic in nature. BC is reported to be the most common cancer in women worldwide, it affects women of all countries belonging to different ethnic groups. Female BC has overtaken lung cancer as the most common diagnosed cancer worldwide. It causes the maximum number of cancer deaths in women globally. BC can also develop in males, but the incidence is very low. According to Globocan (2020) data (Breast cancer fact sheet: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast- fact-sheet.pdf; Sung et al., 2021) the estimated number of new breast cancer cases (both sexes, all ages) in 2020 were 2261419 which accounted for 11.7% of all new cancer cases. The number of deaths due to breast cancer was estimated to be 684996, which constituted 6.9% of the total cancer deaths. The Age-standardised (world) incidence rate for breast cancer was 47.8 and the age-standardised (world) mortality rate was 13.6 for 100,000. An early diagnosis and appropriate treatment makes a substantial difference

in the survival of the patients. Creating awareness on a mass scale, especially in rural population, plays a key role in early diagnosis. As per the International Agency for Research on Cancer (IARC) data on Cancer Survival (The Global Cancer Observatory: https://gco.iarc.fr/survival/survcan), the survival rate of breast cancer patients in India is lower as compared to other countries. In India the 1-year survival is 88.9%, 3-year survival is 66.5% and 5-year survival is 58.8%, whereas the 5-year survival for the USA is 77.4% and for Republic of Korea is 89.4% (the survival rates are based on the cases diagnosed during 2008-2012). The data exhibits the highest survival rate for breast cancer cases as compared to the survival rates of cancer at other sites in the Indian population.The mortality rates have decreased over the years with the advancement in the detection and treatment methods. The treatment methods depend on the molecular classification of the tumour and comprises various combinations depending on whether the BC is localised or has spread to nearby regions or is showing distant metastasis.

2. EPIDEMIOLOGY OF BREAST CANCER

Breast cancer can occur in any woman, belonging to any country at any age after puberty but the incidence rate increases with age. As per WHO factsheets on BC (Breast cancer fact sheet, 2021), in 2020 the number of new BC cases in India were 178361, accounting for 13.5% of all new cases, and the deaths due to breast cancer were 90408 which was 10.6% of all cancer deaths (International Agency for Research on Cancer, 2020: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf). Among cancer cases reported in females, breast cancer accounted for 26.3% of all cancers in India, which is higher than the proportion of BC cases in world.The age-standardised (world) incidence and mortality rates in India are reported to be 25.8 and 13.3 respectively (Globocan, 2020). The IARC "Cancer Tomorrow" (http://gco.iarc.fr/tomorrow/home), predicts that the number of breast cancer cases are going to increase significantly in the coming decades. It shows that globally by 2040 the occurrence of BC will rise by 33.8% and the mortality rate will increase by 51.9% from the 2020 estimated numbers. For India the predicted number of incidences show an increase of 12.7% (2025), 25.9% (2030), 39.2% (2035) and 52.3% (2040), as compared to the estimated 2020 numbers. Similarly, the predicted numbers for mortality due to breast cancer show an increase in 14.2% (2025), 29.4% (2030), 45.6% (2035) and 62.1% (2040). Therefore, by 2040 the estimated number of breast cancer cases would be 271602 and the predicted number of deaths due to breast cancer would be 146522 in India.

As per American Cancer Society 3,53,510 women will be diagnosed with BC in the United States in 2023 and 43,700 will die of it. A survey carried out by the Indian Council of Medical Research (ICMR), New Delhi, shows that the incidence of BC in India has almost doubled from 1982 to 2005. In India the National Cancer Registry Program in 2018 estimated that ~ 1,62,468 new BC cases were diagnosed and ~ 87,090 deaths occurred due to BC (Siegel et al., 2021). As per the data given by Indian Council of Medical Research's National Cancer Registry Programme Report, 2020, the estimated number of incidences of breast cancer cases in 2025 would be 2,32,832. In India the most common cancer in women was cervical cancer in early years of 21st century, but the number of BC cases increased to such an extent that it crossed cervical cancer and became the most common cancer in females by the year 2012. The ICMR 2022 report shows that breast cancer accounts for 28.8% of all the cancers in females. Figure 1 shows the estimated proportions of ten most common cancers in Indian females (Sathish Kumar et al., 2022). The report also mentions that among all cancer sites, breast cancer cases were highest in the age groups of 15-39, 40-64 and 65+ years females accounting for 27.3%, 33% and 23.2% respectively.

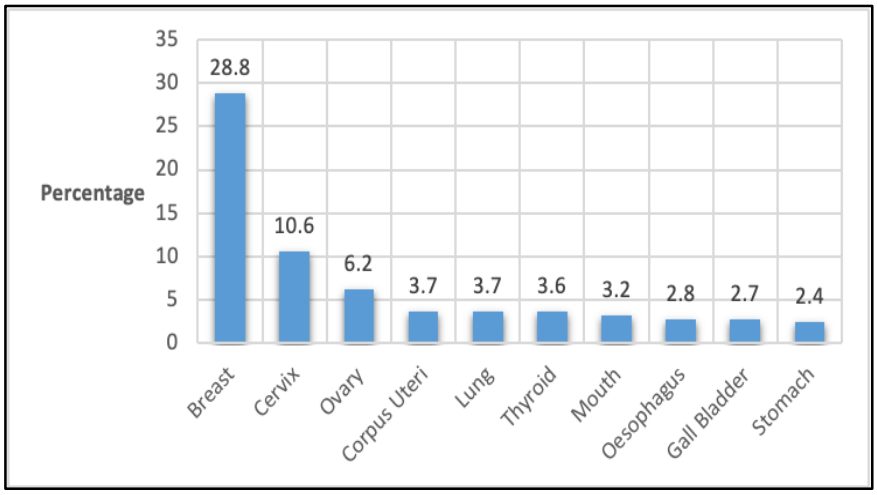
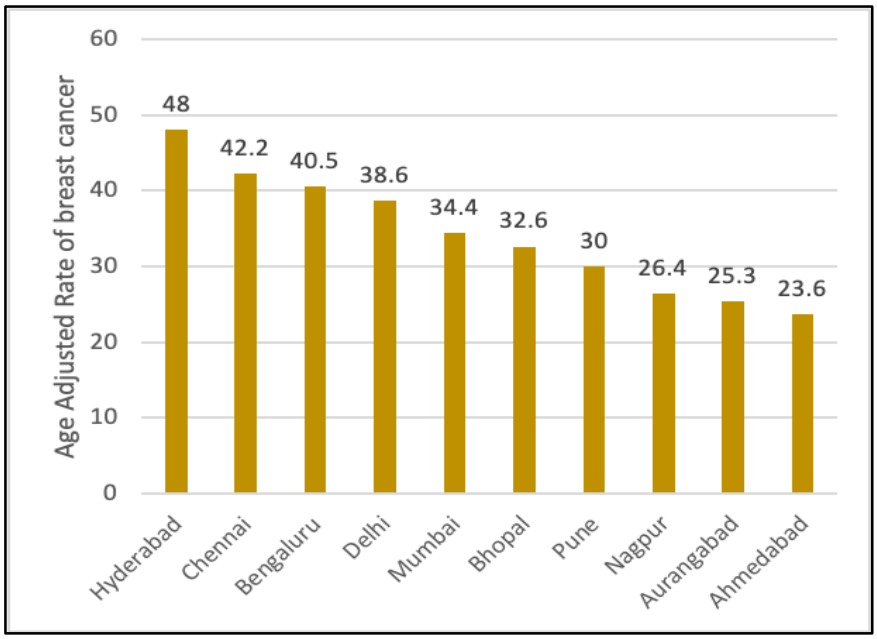


Figure 1: Estimated percentages of ten leading cancer in females, India (Data source: ICMR report, 2022)

India shows distinct variations in number of breast cancer cases with respect to regions and urban-rural populations. As per the latest state-wise data projections for 2020 (Lok Sabha response on breast cancer, 10th February, 2023), the highest age-adjusted rate (AAR) of BC incidence was found in Kerala (45.7), Punjab (43.4), Andhra Pradesh (42.6), Karnataka (41.1) and Telangana (40.2). Age-adjusted rate (AAR) for incidence is the number of females detected with breast cancer per one lakh of women population. The AAR for India was projected to be 31.3 in 2020. Figure 2(a) shows the AAR of breast cancer incidence in some metro cities of India. The data based on the Population-Based Cancer Registries (PBCR) and Hospital Based Cancer Registries (HBCR) shows that the incidence of breast cancer is very high in metro cities as compared to the rural populations. The prevalence was reported to be highest in the districts of Hyderabad, Chennai, Bengaluru and Delhi. Figure 2(b) shows the number of breast cancer cases in different states and union territories of India.



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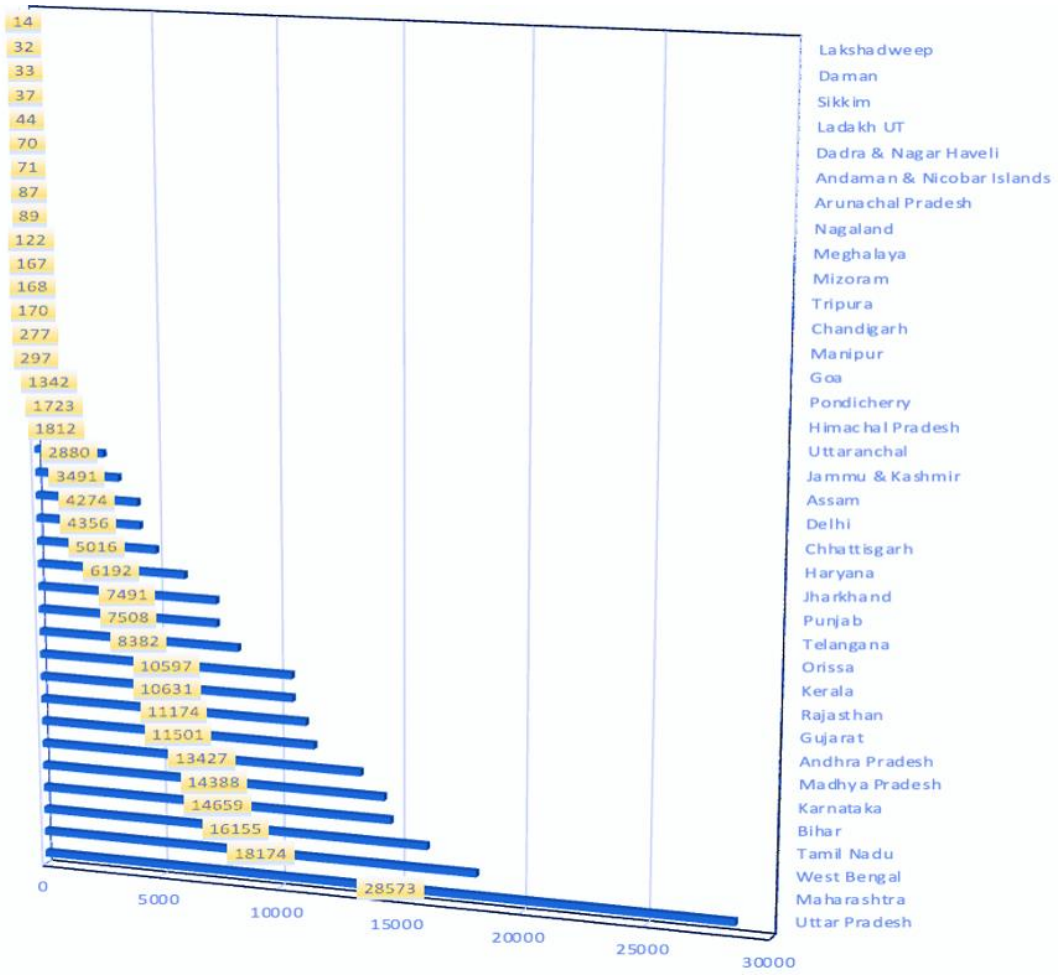


(b)

Figure 2: (a) The estimated breast cancer cases per lakh women in some metro cities of India showing highest numbers. (Data Source: ICMR Report, 2020). (b) Estimated incidences of female breast cancer in India, state wise, (2020). (Data Source: Lok Sabha response on February 10th, 2023).

In USA the median age of females at the time of diagnosis is 62 years (Rojas & Stuckey, 2016). BC predominantly occurs in middle and old age female. The median age of BC patients in India is very different from the western countries. High incidence of BC in urban India is reported in the age group of 40-49 years whereas that in rural India is reported in the age group of 65-69 years. As per the report of ICMR 2021, based on the Hospital Based Cancer Registries, incidence of breast cancer is reported in women of <20 years of age to 85+ years. Figure 3 shows the age group wise distribution of breast cancer cases in India. The highest number of cases belong to the age group of 45-49 years. The data clearly shows that 46% of breast cancer cases included in this report belonged to women of < 50 years of age. As per this data the mean age for occurrence of breast cancer in Indian women is 51 years. Several studies have been reported which show the occurrence of breast cancer at younger age in Indian populations (Thangjam et al., 2014, Malvia et al., 2017). The survival rate of BC patients is poor in India as compared to Western countries due to earlier age at onset, late stage of disease at presentation, delayed and inadequate treatment (Maurya & Brahmachari, 2018; Loibl et al., 2021; Hong & Xu, 2022).

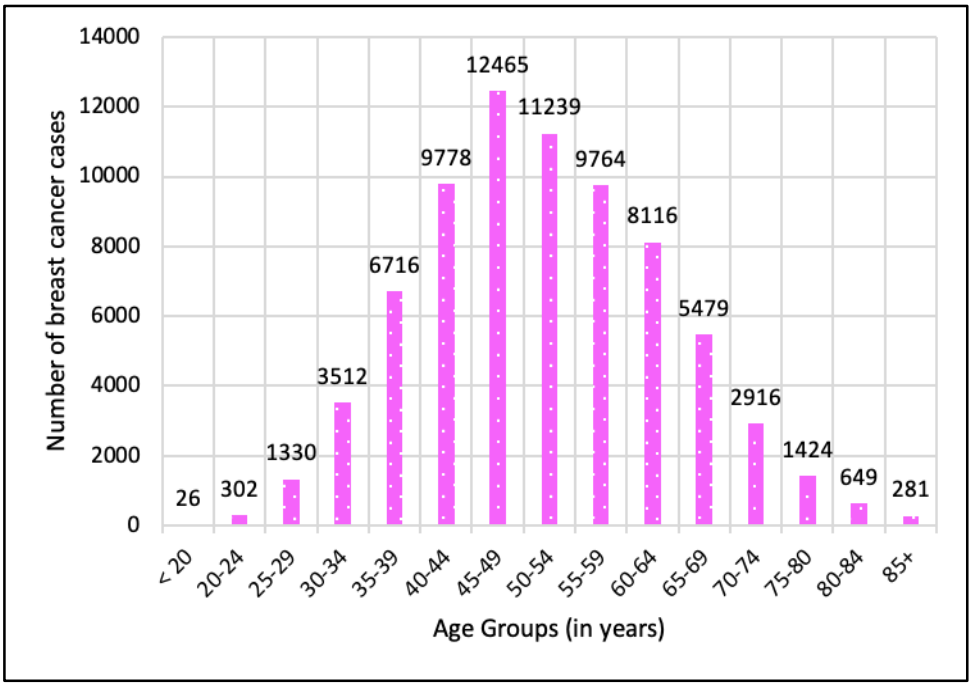


Figure 3: Distribution of breast cancer cases in different age groups of Indian females. (Data Source: ICMR Report, 2021)

3. RISK FACTORS FOR BREAST CANCER

There are various factors which play an important role in development of BC (Hamajima et al., 2002; Gierisch et al., 2013; Sun et al., 2017). These significant factors include both modifiable factors and non-modifiable factors. Non-modifiable factors include age, early menarche, late menopause, late or no pregnancy, family history of breast cancer, gene mutations, dense breast tissue, benign breast disease and previous radiation treatment. Some factors such as hormone replacement therapy, less breast feeding, obesity, less physical activity, use of alcohol, smoking, use of oral contraceptives, and exposure to chemicals/radiation are modifiable. Women with increased BC risk can opt for preventive measures like lifestyle modifications, lower the use of alcohol etc. They also have options like surgery and medication to lower their risk of BC (Britt et al., 2020).

4. CLASSIFICATION OF BREAST CANCERS

Breast cancer can be classified in different ways.

4.1. Histological Classification

Breast cancers mostly develop in the breast, which is made up of ducts and lobules. Based on their origin (ductal or lobular) and nature (*in-situ* or invasive), breast cancers are histologically divided into following types (Figure 4):

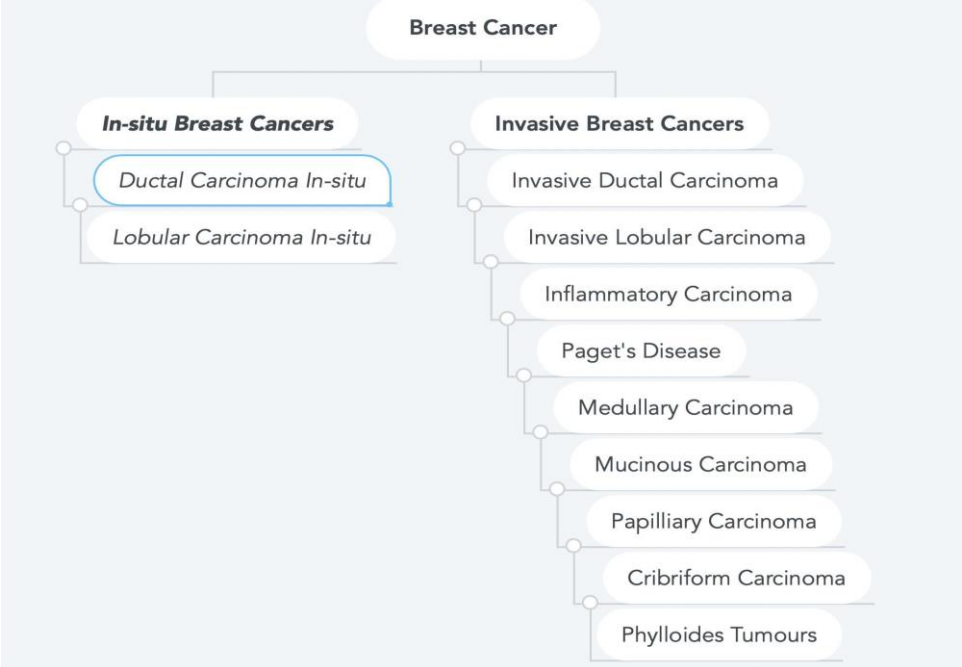


Figure 4: Histological classification of breast cancer.

4.2. Molecular Classification

Molecular classification of invasive breast cancer is based on few genes mRNA expression levels (Dai et al., 2015). One of the pioneer studies on molecular classification was done by Perou et. al. in 2000. Based on the microarray gene expression data, they classified invasive breast cancers into four molecular subtypes - Luminal, HER2-enriched, Basal-like and Normal Breast-like. The Luminal group was further divided into two subgroups - Luminal A and Luminal B. Later on, several studies reported that the normal breast-like subtype was due to contamination of normal mammary glands tissue and it was removed from the list. Further, in 2007 a 5th intrinsic subtype was added which, on the basis of its molecular characteristics, was named as Claudin-low breast cancer (Fougner et al., 2020). The various types of invasive breast cancer on the basis of molecular classification are summarised in Figure 5.

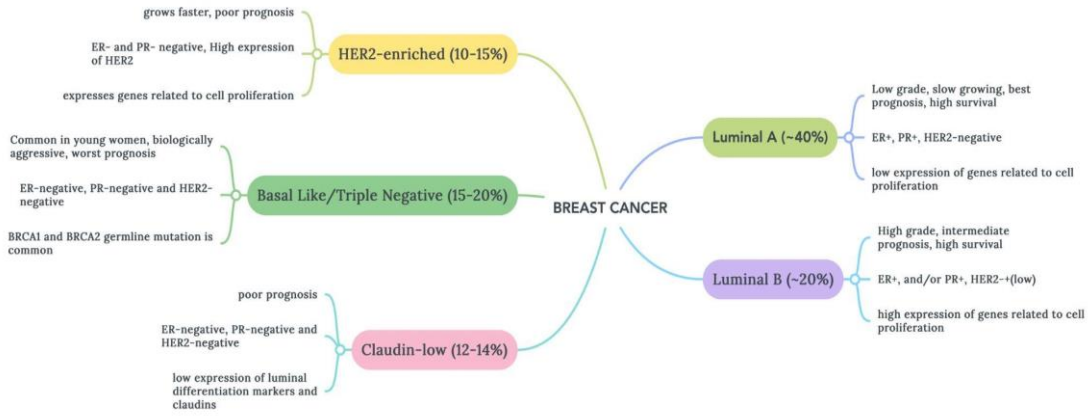


Figure 5: Molecular classification of invasive breast cancers.

5. GENES INVOLVED IN BREAST CANCER

About 10-15% of BC are familial in nature. The genetic variation found in BC patients can be categorised into gain-of-function mutations in protooncogenes and loss-of-function mutations in tumour suppressor genes (Lefebvre et al., 2016). Mutations in many other genes have been linked to BC (Hu et al., 2021), these genes can be categorised as high penetrance (eg. BRCA1, BRCA2, TP53, PTEN, CDH1, STK11), moderate penetrance (eg. PALB2, CHEK2) and low penetrance (eg. ATM, NF1) (Angeli et al., 2020; Breast Cancer Association Consortium et al., 2021). Studies show that mutations in two key important genes i.e. BRCA1 and BRCA 2, are associated with high risk (about 72% and 69%, respectively) of developing BC by 80 years of age (Deng, 2006). Table 1 gives an account of few of the genes involved in BC occurrence, their chromosomal location and cellular functions:

Table 1: Genes associated with breast cancer

Sl. No.	Name of the gene	Chromosome Location	Functions
1	BRCA1	17q21.31	DNA repair, cell cycle control
2	BRCA2	13q13.1	DNA repair, cell cycle control
3	TP53	17p13.1	DNA repair, cell cycle control, apoptosis, senescence
4	CDH1	16q22.1	Regulation of cellular adhesion
5	PTEN	10q23.31	Cell cycle control
6	STK11	19p13.3	Cell cycle control
7	ATM	11q22.3	DNA repair
8	PALB2	16p12.2	DNA repair
9	BRIP1	17q23.2	Interacts with BRCA1, DNA repair
10	CHEK2	22q12.1	Cell cycle control
11	XRCC2	7q36.1	DNA repair
12	RAD51	15q15.1	Homologous recombination
13	ERBB2	17q12	Kinase
14	RB1	13q14.2	Cell cycle regulation
15	CCND1	11q13.3	Cell cycle
16	GATA3	10p14	Transcription factor
17	AKT2	19q13.2	Kinase
18	CASP8	2q33.1	Apoptosis
19	MAP3K1	5q11.2	Kinase
20	SMARCD1	12q13.12	Chromatin remodelling

With the availability of various commercial multiplex assays like BROCA, ColoSeq, Breast Next, Breast Cancer High Risk Panel (Gene Dx), Breast Cancer Susceptibility, etc., which test for a panel of genes including high-penetrance genes, moderate-penetrance genes for BC along with some other low-penetrance genes (Shiovitz & Korde, 2015; Buys et al., 2017), we get to know about the risk of development of breast cancer in an individual.

6. SYMPTOMS OF BREAST CANCER

Some of the major symptoms that are associated with breast cancers include lump in breast, swelling of all or part of the breast, skin irritation or dimpling, pain in breast or armpit area, nipple pain or the nipple turning inward, redness, thickening of the nipple or breast skin, nipple discharge, lump in the underarm area and change in the shape and size of breast. Many times the patients don't show any of these symptoms but get to know about the disease through screening process.

7. SCREENING AND DIAGNOSIS OF BREAST CANCER

Early diagnosis of breast cancer is very important for the successful treatment. The main diagnostic procedures include self-breast examination and clinical examination, mammography, breast ultra-sound, breast magnetic resonance imaging (MRI), biopsy, and positron emission tomography (PET).

Today because of the awareness, a significant number of breast tumours of detectable size can be diagnosed on self-examination (Gupta et al., 2015). Further the clinical examinations are done to confirm the presence of tumour. Mammography is a specialised medical imaging that uses a low- dose X-ray system for scanning the breasts and helps in early detection and diagnosis of BC (Pisano et al., 2005). Diagnostic mammography is used to evaluate the abnormal clinical findings. Screening mammograms are administered in women who have no apparent signs or symptoms of BC (Peairs et al., 2017). These are recommended in women above 40 years of age and even earlier for women who have a positive family history of BC. The population mammography screening recommendations for women with average risk shows lot of variation between countries. In America the recommendations are - annual screening for 40–54 years aged women and a biannual screening for women of more than 55 years. European recommendations specify mammography every 2–3 years in women aged 45–74 years. The National Cancer Grid, India, recommends screening mammography every two years for women aged 50-75 years. With the recent advancements in this technique including Digital mammography, 3D-Mammography and Computer-aided detection, the detection methods have improved and are more specific and sensitive. In 3D-Mammography images are taken from different angles around the breast and then the computer builds a 3-D-like image. Breast ultrasound is a safe (no use of radiation) and non-invasive method, which is used to produce pictures of internal structures of the breast. It is used to diagnose breast abnormalities found during a physical examination, mammogram or breast MRI. Ultrasound is especially useful in patients with dense breast tissues. It is reported that in women with dense breasts, the sensitivity of mammography was found to be 50%, and that of mammography plus ultrasound was increased to 77.5% (Berg et al., 2008). Breast ultrasound is also required for carrying out ultrasound-guided biopsy of breast tumours whose normal biopsy cannot be performed. Breast MRI has the highest sensitivity for breast cancer detection (> 90%). It provides information about the extent of the disease. It may be used to screen women at high risk of BC (Lehman & Smith, 2009; Morrow et al., 2011). The MRI screening of breast is not very specific, therefore, it results in high number of false positives. The next step is histologic diagnosis of the biopsy which is carried out to find out type of

breast cancer, grade of breast cancer and determination of ER, PR and HER2- receptor status. The biopsy may be core needle biopsy or fine needle aspiration cytology (FNAC). A positron emission tomography (PET) scan is not used for screening of BC. It is an imaging technique used to trace the spread of BC, whether the cancer is showing axillary or extra axillary lymph nodes metastasis or distant metastasis. Nowadays PET combined with Computer Tomography (PET/CT Scan) has further improved the detection sensitivity. PET scans are also used to assess the treatment response. Figure 6 describes the basic steps involved in screening and diagnosis of breast cancer. On the basis of the results of all these criteria the clinicians decide the most suitable treatment options for the patients. The correct diagnosis of breast cancer is of immense importance as the treatment options are based on the Stage, Grade, biomarkers etc.

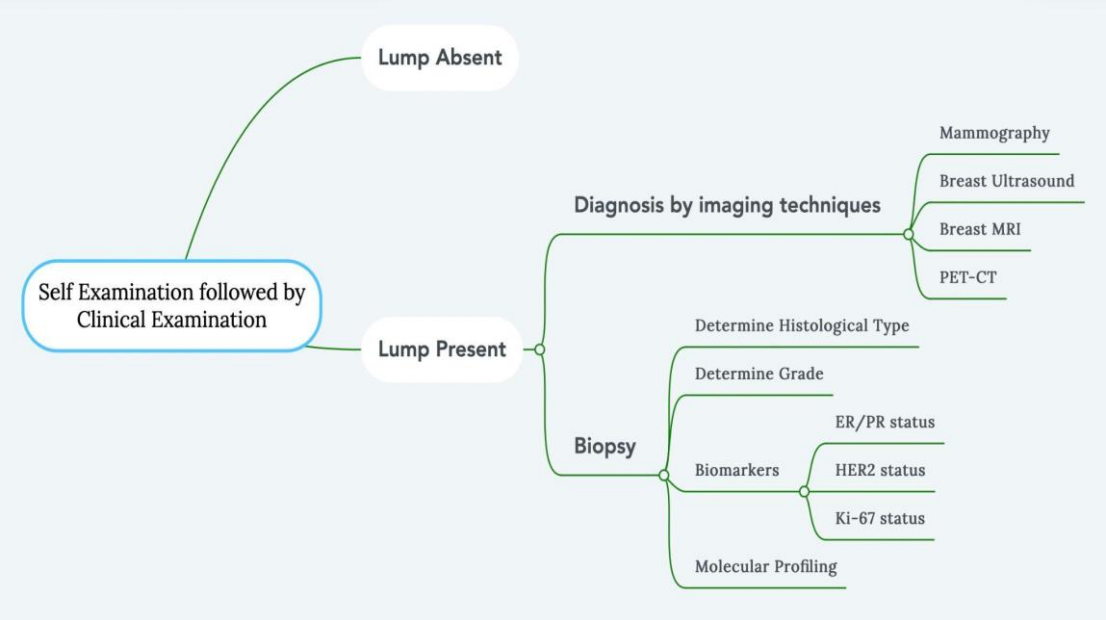


Figure 6: Steps involved in screening and diagnosis of breast cancer.

7.1. Staging of Breast Cancer

The staging of BC is very important in deciding the line of treatment. The staging is based on the size of tumour, nature of tumour (invasive or non-invasive), involvement of lymph nodes and involvement of any other organ. Internationally the most accepted system i.e. American Joint Committee on Cancer Classification (AJCC), described the classification based on TNM, where T represents the tumour size, N represents the involvement of lymph nodes and M shows the metastasis to other organs. In 2018 the 8th edition of the AJCC staging manual was published, it outlines a new prognostic staging system for BC where immunohistochemical markers and expression of other genes were also taken into account. Nowadays the clinicians define the prognosis on the basis of factors like status of Estrogen Receptor, Progesterone Receptor, HER2; grade and multigene assays.

The stages of BC ranges from 0-IV i.e. Stage 0, Stage I (IA and IB), Stage II (IIA and IIB), Stage III (IIIA, IIIB and IIIC) and Stage IV (AJCC, 2018). The details of all these stages are summarised in Table 2:

Table 2: AJCC TNM Staging System for Breast Cancer

Stage of Breast Cancers	Sub-category	TNM	Remarks
Stage 0		T_{is} N_0 M_0	T_{is}- Ductal carcinoma *in-situ;* N_0- no involvement of lymph nodes; M_0- no metastasis
Stage I	A	T_1 N_0 M_0	T_1- tumor $\leq$ $\leq$ 20mm
	B	T_0/T_1 N_{1mi} M_0	mi- Micrometastasis to regional lymph nodes
Stage II	A	T_0/T_1 N_1 M_0; T_2 N_0 M_0	T_2- tumor $\geq$ $\geq$ 20mm but $\leq$ $\leq$ 50mm; N_1- limited metastasis to regional lymph nodes (1-3)
	B	T_2 N_1 M_0 ; T_3 N_0 M_0	T_3 – tumor $\geq\geq$ 50mm
Stage III	A	T_0/T_1/T_2/T_3 N_2 M_0	N_2- moderate metastasis to regional lymph nodes (4-9)
	B	T_4 N_0/N_1/N_2 M_0	T_4 – tumor (any size) with extension to chest wall and/or skin
	C	Any T N_3 M_0	N_3- significant metastasis to regional lymph nodes (> 9)
Stage IV		Any T Any N M_1	M_1 – Distant metastasis

7.2. Grading of Breast Cancer

Breast cancers are classified into different grades i.e. Grade 1, Grade 2 and Grade 3, based on the morphologic features which show how different the cancer cells are from the normal cells and also how fast are they growing. The histologic grading of BC is done mostly by the Nottingham grading system. This grading system is Elston-Ellis modification of Scarff-Bloom-Richardson grading system (Bloom & Richardson, 1957). The Elston & Ellis grading system (1991) takes into account the mitotic index of the tumor, the nuclear morphology and the differentiation of the cells (formation of tubules). The different Grades of BC are summarised in Table 3.

Table 3: Nottingham Grading System for Breast Cancer (Elston & Ellis, 1991)

Sl. No.	Criteria	Score	Remark
1	Mitosis Count	1	0-7 mitosis/10HPF
		2	8-14 mitosis/10HPF
		3	>15 mitosis/10 HPF
2	Nuclear atypia	1	Regular nuclei similar to normal cells
		2	1.5-2 times the size of normal nuclei and variability
		3	> 2 times the size of normal nuclei and polymorphic
3	Tubule formation	1	> 75% of tumor shows tubule formation
		2	10 - 75% of tumor show tubule formation
		3	< 10% of tumor show tubule formation

For each category a score of 1-3 is given where a score of 1 is most favourable and a score of 3 is least favourable. Grade 1 corresponds to the combined scores of 3 – 5. Grade 1 BC are well differentiated, look like normal cells and are usually slow growing. Grade 2 corresponds to a combined score of 6 or 7. Grade 2 BC are moderately differentiated, look like normal cells and are faster growing. Grade 3 corresponds to a combined score of 8 or 9. Grade 3 BC are poorly differentiated, look different from normal breast cells and are fast growing and aggressive in nature.

7.3. Biomarkers

For patients with invasive breast cancer the determination of the following biomarkers is mandatory: status of *ER* (estrogen receptor), *PR* (progesterone receptor) and *ERBB2/HER2* (epidermal growth factor 2) (Hammond et al., 2010; Wolff et al., 2013; Elster et al., 2015). These biomarkers are tested by the technique of immunohistochemistry or fluorescent *in-situ* hybridisation, using paraffin sections or cryosections of tumour samples. In most of the countries positive staining in >1% of the tumour cells is considered hormone receptor positive i.e., ER^+ and PR^+, whereas a positive staining in $\geq\geq$ 10% tumour cells is relevant for HER2-positive status. In case of ER-positive and HER2-negative BC another biomarker Ki67 is also tested which shows the proliferation rate and is also useful in predicting the chemosensitivity. If $\geq\geq$ 20% cells show positive staining for Ki67 they are considered to be highly proliferating (Ellis et al., 2017).

7.4. Molecular Profiling of Breast Cancer

Molecular profiling of BC provides additional prognostic information and also predicts the response to therapy. They provide an overall risk assessment of BC reoccurrence in patients with early stage breast cancer (Vuong et al., 2014). Some of these tests provide a Reoccurrence Score. These tests also estimate the extent of benefits (benefit or little or no benefit) of chemotherapy for patients, thereby protecting patients from overtreatment. Some of the commonly used genome biomarker assays are:

1. Oncotype DX - 21 gene real time PCR based assay
2. PAM50 – 50 gene quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assay
3. MammaPrint70 – 70 gene analysis using cDNA microarrays
4. Blueprint – 80 gene analysis used for subtype classifier
5. MammaTyper -reverse transcription quantitative real-time polymerase chain reaction of ER, PR, Ki67 and HER2 genes
6. Endopredict – 12 gene assay
7. BreastOncPx- 14 gene RT-PCR assay
8. Breast PRS – 200 gene assay

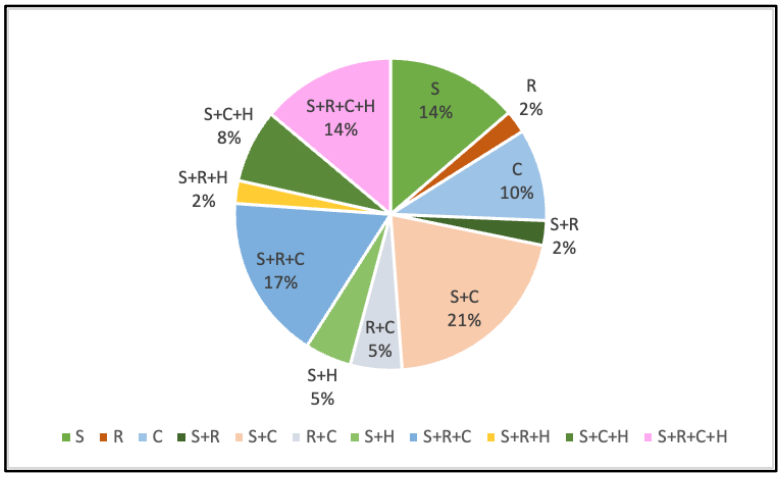
The genes analysed in these genome biomarker assays provide information about the biology of tumour, tumour progression, invasion, metastasis, cell-cycle regulation, angiogenesis etc. (McVeigh et al., 2014; Sparano et al., 2018; Pu et al., 2020). Initially these earlier tests like PAM 50, MammaPrint etc. were informative in making treatment decisions for early stage

BC only but now they also help in making treatment decisions for the advance stage BC. The National Cancer Institute (NCI) sponsored clinical trials like TAILOR$_x$ [[The Trial Assigning Invidualized Option for Treatment (R_x)]] included patients with ER-positive and lymph node negative breast cancer. The results based on follow-up studies of ~10,000 patients showed that adjuvant hormone therapy alone worked equally well as hormone therapy and chemotherapy together. Thus, a test which quantifies the expression of certain genes with a RS (Recurrence Score) can predict which women can safely avoid chemotherapy. Another NCI trial, the R_xPONDER (A Clinical Trail R_x for Positive Node, Endocrine Breast Cancer) found that the same 21 gene expression test can also be used to design treatment options for women with more advanced breast cancers. The study showed that if the recurrence score is low in some postmenopausal women with HR^+, HER2-negative breast cancer which has spread to several lymph nodes, the hormone therapy alone is effective and they do not benefit from chemotherapy when added with hormone therapy.

8. TREATMENT

According to the World Cancer Report 2020, early detection and rapid treatment is the most efficient strategy for the control of BC. The treatment plans are recommendations based on various guidelines like National Comprehensive Cancer Network (NCCN) guidelines, European Society for Medical Oncology (ESMO) guidelines, Japanese Breast Cancer Society (JBCS) guidelines, Chinese Anti-Cancer Association (CACA) guidelines etc. In 1996, the National Comprehensive Cancer Network (NCCS), published its first set of Clinical Practice Guidelines in Oncology. Thereafter, NCCS Clinical Practice Guidelines in Oncology are posted with the latest update date and version number (eg. Breast Cancer, Version 1.2023). These guidelines are used by the clinicians universally in planning the treatment options for the patients. The clinicians decide on the treatment options when all the information related to tumour: tumour size, its location, Stage, Grade, hormone receptor status, Molecular profile (Prat et al., 2015), genomic test results and recurrence score is available to them (Waks & Winer, 2019). The clinicians also take into consideration the patients age, general health conditions, menopausal status and preferences in finalising the treatment course. In the present day the concept of “personalised treatment” is gaining importance (Tuasha & Petros, 2020; Gennari et al., 2021). The treatment options available for BC include localised and systemic therapies. The main treatment options include: surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy and targeted therapy (Hu et al., 2017). Few of the key decisions which have to made at the beginning of the treatment include whether to opt for adjuvant (after surgery) or neoadjuvant (before surgery) therapy and also to decide on breast conservation surgery versus mastectomy. A 2018 systematic review of studies reported that earlier diagnosis of BC can lower the treatment costs (Sun et al., 2018).

In India the main treatment options of breast cancer include surgery, radiation, chemotherapy and hormonal therapy. The data shared by ICMR in its 2021 report based on the Hospital Based Cancer Registries clearly shows that the treatment options vary on the basis of spread of the disease. Figure 7 depicts the treatment options for localised, locoregional and distant metastasis breast cancer.



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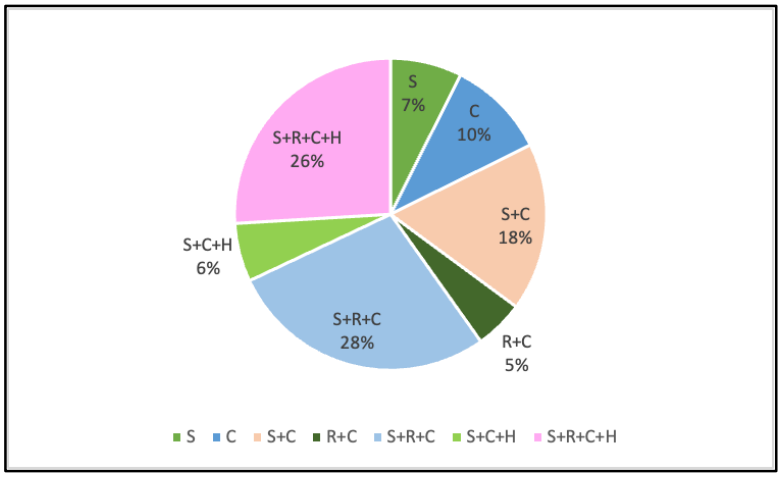
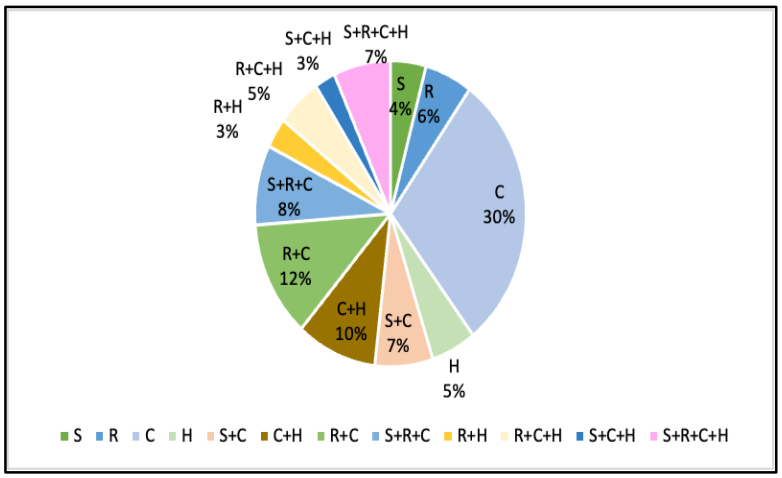


(b)



(c)

Figure 7: Breast cancer treatment options in India based on the clinical extent of the disease. Early Breast Cancer, (b) Locally Advanced Breast Cancer and (c) Advanced Breast cancer. (S- Surgery, R- Radiation therapy, C- Chemotherapy and H- Hormonal therapy; Treatment options of >2% values are only included in the charts.) (Data Source: ICMR Report, 2021)

8.1. Surgical Treatment Options

Breast surgery has been used as a treatment option since the time BC is known. In 1894 William S Halsted (USA) published his landmark paper on Radical mastectomy which was modified but remained the standard of care until 1980s. In 1948, Patey and Dyson (London) introduced the modified radical mastectomy. In the early 1970s, Umberto Veronesi (Italy) and Bernhard Fisher (USA) led separate teams, developed the concept of breast conserving surgery. Their results showed that the long term survival of women with early BC who were treated breast conserving surgery and postoperative radiotherapy was similar to rate as radical mastectomy (Veronesi et al., 1995). Surgery for BC has undergone tremendous change over the past twenty years. In patients with early BC the clinicians make the choice of surgery depending on the size of tumour, position of tumour, clinical manifestation of tumour and patient's choice (Fisher et al., 2002).

Surgical options include: Mastectomy or Breast Conserving Surgery (BCS). A mastectomy is a surgical procedure to remove some part or all of breast tissue (Freeman et al., 2018). Mastectomy is often associated with immediate breast reconstruction. BCS enables the removal of the cancerous tissue and many times it is combined with simultaneous preservation of intact breast tissue called oncoplasty (Piper et al., 2015). The removal of affected lymph nodes is done by sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) (Freeman et al., 2018).

There are several types of mastectomy such as total mastectomy (removing the entire breast tissue), double mastectomy (removing both breasts), radical mastectomy (removing the entire breast, the underarm lymph nodes and the chest wall muscles), modified radical mastectomy (removing the entire breast and underarm lymph nodes), skin sparing Mastectomy (removing the entire breast and nipple but leaving the skin intact) and nipple sparing mastectomy (leaving the skin, nipple and peripheral breast tissue)

Breast Conserving Surgeries include lumpectomy (removing the tumour and the surrounding tissue) and quadrantectomy (removing the tumour and more breast tissue than lumpectomy).

8.2. Radiation Therapy

Radiation therapy uses high energy rays to kill the cancer cells. Radiotherapy may be administered as adjuvant radiation therapy or neoadjuvant radiation therapy. It is a localised treatment of breast cancer which is done usually after surgery and/or chemotherapy (Darby et al., 2011). Radiation therapy has shown significant improvement in the survival rates of BC patients and it also minimises the possibility of recurrence (Yang & Ho, 2013).

There are several different types of radiation therapy such as external-beam radiation therapy (most common type, radiation given by machine outside the body), intra-operative radiation therapy (radiation given during operation to the area from where tumour was removed), partial breast irradiation (radiation is given only to the tumour area, usually used after lumpectomy), intensity-modulated radiation therapy (intensity of radiation is varied for better results), brachytherapy (done by placing a radioactive source inside tumour) and proton therapy (uses protons instead of X-rays).

Radiation therapy is usually given 5 days a week for 1-7 weeks. The most common side effects of radiation therapy observed in BC patients include: skin irritation, darkening of the skin exposed to radiation, fatigue, lymphoedema and sometimes blistering of the exposed skin. These get back to normal conditions in few months.

8.3. Chemotherapy

Chemotherapy is being used as a therapeutic measure to treat BC since 1970s. It may be given before the surgery (neo-adjuvant) with the aim to shrink the tumour or after the surgery (adjuvant) to reduce the chances of cancer coming back. Neoadjuvant chemotherapy is used for locally advanced BC. Chemotherapy includes anti-cancer drugs which can be given intravenously or orally. It is most effective when more than one drug is given. Chemo is given in cycles (usually 6-8 cycles), followed by a rest period (15-21 days) which gives the body time to recover (Harbeck & Gnant, 2017; Waks & Winer, 2019).

Over the years, different chemotherapeutic combinations have been developed like AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide), CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil), CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil), TAC (docetaxel, doxorubicin and cyclophosphamide), EC-paclitaxel (epirubicin and cyclophosphamide followed by paclitaxel), etc.

Chemotherapy is very effective but it has a harsh effect on the patient's body. The common side effects observed in patients undergoing chemotherapy include hair loss, loss of appetite, nausea/vomiting, mouth sores, fatigue, discolouration of nails, anaemia, leukopenia, change in skin colour, diarrhoea and increased susceptibility to infections. Besides these, there are other less frequent side effects including cardiomyopathy, neuropathy and impaired mental functions. Chemotherapy also disrupts the menstrual cycle and causes fertility issues in young women.

8.4. Hormonal Therapy

Hormonal therapy or Endocrinal therapy is used either as an adjuvant or neoadjuvant therapy in breast cancer patients which are positive for estrogen receptors (ER^+) or progesterone receptors (PR^+) (Lumachi et al., 2011; Tremont et al., 2017). The expression of ERs/PRs are very common and present in ~70% of invasive breast cancers. In hormonal treatment the receptors are blocked and/or the levels of estrogen are lowered. Drugs like Tamoxifen, Toremifene, Fulvestrant are used to block or degrade ERs while aromatase inhibitors like Letrozole, Anastrazole, Exemestane are used to lower the estrogen levels (Goss et al., 2011). Ovarian suppression by leuprolide (Lupron) and goserelin (Zoladex) is also an option for pre-menopausal women. Hormonal therapy combined with chemotherapy has shown to reduce mortality rates amongst breast cancer patients. The duration of hormone treatment is for 5-10 years. The selection of the drug depends on the menopausal status of the women. These can be given as injections or orally. The common side effects of these drugs include- night sweats, hot flashes, vaginal dryness, weak bones, mood swings, headache, joint and bone pain (Krauss & Stickeler, 2020).

8.5. Targeted Therapy

Targeted therapy (Biological Therapy) is a relatively new step in cancer treatment which was introduced in the regime of treatments in the first decade of the 21st century. Targeted therapy uses drugs that target specific proteins on BC cells which help them grow and metastasise. These drugs either kill the cancer cells or slow down their growth (Higgins & Baselga, 2011). Targeted therapy can include the use of antibodies, vaccines and gene therapies. It can be administered as neoadjuvant therapy or as adjuvant therapy. The most commonly used therapy is in human epidermal growth factor receptor 2 (HER2-) positive breast cancer patients, which constitute ~15-20% of BC. *HER2* or *HER2/neu* is a transmembrane receptor tyrosine kinase in the epidermal growth factor receptor (ERBB2) family and is associated with poor prognosis. Patients showing overexpression of ERBB2 benefit from the targeted

therapy, including anti-*ERBB2* antibodies (trastuzumab and pertuzumab) (von Minckwitz et al., 2017) and small-molecule tyrosine kinase inhibitors (lapatinib and neratinib).

Currently, targeted therapy exists for HER2-positive, ER^+/PR^+, HER2-low, TNBC (Triple Negative Breast Cancer) and BRCA mutated breast cancers. In recent years, targeted therapy is added for treatment along with hormone therapy. Like in case of HER2-negative breast cancer patients, mTOR inhibitor (Everolimus) is given along with exemestane in pre-menopausal women, while post-menopausal women often receive CDK 4/6 inhibitor (Palbociclib or Ribociclib) in combination with hormonal therapy (Finn et al., 2016; Dickler et al., 2017). Drug Atezolizumab is approved for treatment of triple-negative breast cancer and Denosumab is approved in case of BC with bone metastasis. Another drug used as targeted therapy is the poly(ADP- ribose) polymerase (PARP) inhibitors, which is given to HER2-negative metastatic breast cancer patients with BRCA mutations. The drugs of targeted therapy are given orally or intravenously. The main side effects include shortness of breath, diarrhoea, heart problems (Kwapisz, 2017; Terantino et al., 2020).

8.6. Immunotherapy

Immunotherapy is a new treatment option for BC where the body's immune system is used to fight the cancer cells. PD-1 inhibitors (immune checkpoint inhibitor) are used as a treatment drug in BC. Pembrolizumab (a PD-1 inhibitor) targets the PD-1 protein of the immune system thereby boosting the immune response against BC cells (Sabatier et al., 2015). Immunotherapy has shown good results in treating early stage triple negative breast cancer and also in some metastatic breast cancers (Tolba et al., 2021). Immunotherapy drugs are given intravenously in a time period of usually 3-6 weeks. The side effects of immunotherapy include nausea, cough, fatigue, skin rash, diarrhoea, fever, chills and sometimes autoimmune reactions.

9. CONCLUSION AND FUTURE PROSPECTS

The estimated projections show that 3.03 million new breast cancer cases will be diagnosed worldwide by 2040 and 1.04 million females will die of it. In some developing countries the numbers are expected to increase further due to improvements in the awareness, detection and registration systems. BC is one of a few cancers for which an effective screening test is available and with the technological advances in imaging, new opportunities for improvements in both screening and early detection are gaining importance. BC is a treatable disease if detected early. We need effective awareness programmes; screening and treatment methods to reduce the mortality caused by BC. As cancer treatment is becoming more individualised, researchers are looking at ways to personalise BC screening based on the patient's genetic makeup, family history and other risk factors. Genomic analyses have provided more insights into the molecular diversity of BC which eventually will help in identifying more BC subtypes and designing specific treatment strategies. The goals of the personalised medicines will be achieved with new target therapies which should be more effective and less toxic to the patient. A number of new drugs have been discovered in recent years to treat breast cancer based on the knowledge in the field of immunology and molecular biology. Molecular diagnostic assays, which are integrated as a part of present day BC management, are very informative as they estimate risk of metastasis, tumour recurrence and also the response to therapy. These informations save the patients from overtreatment.

Globally, the data shows that the survival rate in different countries shows a huge disparity, major reason being unavailability of diagnostic techniques and unaffordable treatments. Thus ensuring access to standard diagnosis, including imaging techniques and histopathology, and treatment

methods, including surgery, radiation, chemotherapy and hormonal therapy, to all breast cancer patients is of utmost importance. In India, the National Cancer Registry Programme (NCRP) under ICMR has been operational since 1981. NCRP collects data through Population Based Cancer Registry (PBCR) and Hospital Based Cancer Registry (HBCR). Cancer registries play a very important role as they provide an estimate of the cancer cases in future so that out health care systems can take appropriate steps to deal with it. One of the major drawbacks of these cancer registries is that they cover only a limited proportion of the population. Presently NCRP covers 16.4% of Indian population, which constitutes 31.6% coverage of urban population and only 9.5% coverage of rural population. We need to have more numbers of rural based PBCRs to get cancer based information from all over the country. The ICMR National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) focuses on increasing awareness, early detection and treatment of cancer including breast cancer. Under these health schemes an Indian citizen, above 30 years of age, can get screened for the three common cancers i.e., oral, breast and cervical, at Ayushman Bharat – Health and Wellness Centres. National Cancer Institutes are being set up and oncology facilities in various government hospitals are being improved to manage the detection and treatment process of cancer cases in our country. Another drawback of the BC treatment is its high cost. Availability of Indian generic medicines have brought down the costs of treatment drastically thereby making the treatment more affordable and accessible to a larger group of patients. But still there is a need for the introduction of more generic medicines.

Advances in BC treatments offer women with better treatment options and improved quality of life. The patients will also benefit tremendously if the duration of each treatment is shortened and their side effects are minimised. Early stage BC are highly curable, the main challenge lies with the treatment of metastatic breast cancer, perhaps one day we will be able to get a cure for advanced breast cancer with the availability of better diagnostics and treatments options. Management of BC survivors will play an integral part in raising awareness. Besides the advancement in diagnosis and treatment, the preventive measures hold their own importance. The preventive measures include leading a healthy lifestyle, being aware of family medical histories and doing self-breast examinations on a regular basis since attaining adulthood. Healthy diet and daily physical exercises along with yoga and meditation have proven to be beneficial.

In 2021 WHO established “The Global Breast Cancer Initiative (GBCI)”, which aims to assess, strengthen and scale-up services for the early detection and management of BC. It provides guidance to governments on health systems strengthening for BC with the goal of reducing breast cancer by 2.5% per year. We hope that in future the awareness will increase with more nationwide cancer literacy programmes and with further improvement in the healthcare system the numbers of deaths with breast cancer will reduce.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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