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Awareness Levels and Recent Developments in Breast Cancer Knowledge

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Abstract

Breast cancer is a global public health challenge and, at present, the most prevalent tumor globally. Public awareness, concern, and improvement in breast imaging have had a positive effect on breast cancer recognition and screening. Breast cancer is fatal disease in women and the prime cause of death in women population. Over the last two decades, research pertaining to the breast cancer has led to remarkable progress in our knowledge about the breast cancer, which lead to even more competent treatments. Of all the cancerous diseases, breast cancer is ranked as one of the major causes of death in post-menopausal women responsible for 23% of total cancer deaths. It is a worldwide problem nowadays, yet still it is being diagnosed in their later stages because women are neglecting the self-examination and clinical check-up of the breast. This review covers anatomy of the breast, risk factors, breast cancer epidemiology, pathogenesis of breast cancer, breast cancer stages, diagnostic tests and treatment including chemotherapy, surgery, targeted therapy, hormone replacement therapy, radiation therapy, complementary therapy, gene therapy and stem-cell therapy etc for breast cancer.

Keywords: Breast cancer, Chemotherapy, Gene therapy, Stem cell therapy

Background

Breast cancer is the leading cancer and also the most leading cause of death from cancer in women throughout the World. There were an estimated 1.38 million new cases of breast cancer in 2008 with nearly 50% of all patients with breast cancer and nearly 60% of deaths worldwide happening in developing nations. There is a significant variation in breast cancer survival rates globally, ranging from an estimated 5-year survival of 80% in developed nations to less than 40% for developing nations [1]. Developing nations have resource and infrastructural limitations that compromise the goal of optimizing breast cancer outcomes through early recognition, diagnosis and management [2]. In developed nations such as the United States, approximately 232,340 female will receive the diagnosis and mortality of 39,620 female will occur from breast cancer in 2013 [3]. The lifetime risk to develop breast cancer in an American woman is 12.38% [3]. The impressive decrease in mortality from breast cancer in the United States between 1975 and 2000 is due to continuous improvement in both screening mammography and treatment [4]. As stated by the World Health Organization (WHO), improving outcome and survival from breast cancer through early detection is still the cornerstone of breast cancer policies. Various contemporary drugs are used to treat breast cancer. Medical treatment of breast cancer with antiestrogens like tamoxifen or raloxifene may inhibit breast cancer in people who have an enhanced likelihood of getting it [5]. Bilateral surgery of the breasts is another preventive measure in some heightened

likelihood of getting cancer in women. In patients identified with breast tumor, various management strategies are employed including targeted therapy, hormonal therapy, radiation therapy, surgery and chemotherapy. In those with distant metastasis, management is generally directed at maximizing the quality of life and survival [6]. The uncomfortable side effects of treatments for breast cancer are among the most compelling reasons to look for some alternative treatments. The application of herbs in the treatment of patients with breast cancer is regarded as a natural remedy, since certain plants potentially contain properties that can naturally cure breast cancer [7–11].

Epidemiology

At present, one out of every twelve females in Britain aged between 1 and 85 years develops breast cancer. Breast cancer is prevalent in females and accounts for 18% of all women's cancer. Breast cancer is estimated to grow up to 85 per 100,000 women in 2021 [12]. In 2012, 1.67 million new breast cancer cases were diagnosed that accounts for 25% of all cancers in women. Ferlay et al. [13] reported that 883,000 are in less developed nations and 794,000 in the majority of developed nations. Based on the data, 145.2 Belgian women and 66.3 Polish women between 100,000 have breast cancer [14]. Incidence of breast cancer among United States women is one in eight and In Asia one woman has breast cancer out of 35. In Iran 10 per 100,000 population and 7000 new cases each year have been reported [15]. Incidence of breast cancer is on the rise in Pakistan [16–18]. Breast cancer is detected predominantly in the densely populated regions of South Asian developing countries [19, 20]. Breast cancers in men have been found in Northern regions of Pakistan [21]. Yang et al. [22] reported that recent breast cancer cases in China were 168,013 in the year 2005 and 121,269 in the year 2000.

Anatomy of breast

Both men and women possess breasts [23]. The breast is composed of fatty tissue referred to as adipose tissue [24]. The female's breasts tend to have more glandular tissue than those of the men [25]. Female breasts consist of 12–20 lobes which are subdivided into smaller lobules [26]. The lobes and lobules are linked through milk ducts. The breast adipose tissue is innervated by a plexus of nerves, blood vessels, lymph vessels, lymph nodes, and also contains fibrous connective tissue and ligaments [27]. The female breast is constructed to nourish the infants best and to give sexual pleasure to the woman herself. The breasts are glandular organs that respond very sensitively to the hormonal changes in the body [28]. They undergo cyclic variations in harmony with the menstrual cycle. They are closely related to the female genital system. Nipple stimulation increases secretion of prolactin from the pituitary gland. This hormone also influences the uterus and can induce contractions. Lymph node draining breast tissues is also present in armpits. Once a woman has given birth and her milk begins to come in, mother can develop dramatic swelling under her arms due to engorgement of the breast tissue in her area. Breasts are all different sizes and shapes, and so are nipples. The majority of female have one breast that is slightly smaller than the other [29]. The areola and nipple epidermis is highly pigmented and wrinkled to a certain degree, and the skin of the nipple is filled with a number of apocrine and sebaceous sweat glands and relatively small hair. The 15–25 milk ducts enter the nipple base, wherever they dilate to form the milk sinuses. These milk ducts serve as the milk carriers to the nipples [30]. Slightly under the surface of the nipple, these sinuses end in cone shaped ampullae. The spherical areola is present around the nipple and is between 15 and 60 mm in diameter. Sebaceous glands, sweat glands and lanugo hairs are present on its skin, Montgomery's glands, are big, modified sebaceous glands with tiny milk ducts that open into Morgagni's tubercles in the areola epidermis. Embedded within the nipple and areola, multiple smooth muscle fibers are arranged circularly and radially within dense connective tissue and longitudinally within lactiferous ducts that extend upward into the nipple. The muscle fibers are responsible for emptying milk sinuses, nipple erection, and areola contraction. Most of the parenchyma of the breast extend inferiorly from the location of the 2nd or 3rd rib to the infra mammary fold, which is roughly at the location of the 6th or 7th rib, and transversely from the edge of the

sternum to the anterior axillary line. The mammary tissue also extends irregularly into the axilla as the glandular tail of spence. The posterior aspect of the breast lies on segment of the fasciae of rectus abdominis muscles, pectoralis major's fasciae, external abdominal oblique and serratus anterior.

A global prospective

Globalization, which therefore largely defines our era, was principally associated with commercial-related activities, thereby with environmental issues, and particularly in recent years with the sinister reality of terrorism. Until now the "globalization" of many human being activities, along with health care, has been setting off for a number of decades, improving in conjunction with improvement in information machinery. Right or wrong, planned or not, many clinicians from developing nations monitor what Americans are accomplishing, or are supposed to be accomplishing, as "state of the art" and new best performance that should be emulated. The steps examined and our present account with bone marrow transplantation suggests that current "standard of care" United States reported interventions are not suitable to international use. Unfortunately, widespread lack of community well-being measures to breast cancer has rendered such understanding of rights for women impossible. Unrealistic, fatal, and very costly breast cancer treatments are unable to help the vast number of women on the planet at risk for or who get breast cancer [31].

Types of breast cancer

It is categorized based on location into invasive and non-invasive breast cancers.

Non-invasive breast cancer

It is a cancer that has not spread outside the lobule or ducts where it lies [32]. Ductal carcinoma in situ is an example of a type of non-invasive breast cancer. Ductal carcinoma in situ manifests when abnormal cells form inside the milk ducts, but not moved to close tissue proximity or beyond. The term "in situ" refers to "in place." Although the abnormal cells have not moved to tissues beyond the lobules or ducts, they are able to evolve and develop into invasive breast cancer. The background of each scientific unit is normal and is demonstrated, and a biological appreciation of the available information is provided. Lobular carcinoma in-situ is appreciated as just a risky sign moderately rather than a precursor for the subsequent development of invasive cancer, so once the judgment is reached, further operative input is preventable and sequential follow-up only is recommended. The treatment of ductal carcinoma in-situ must be remembered that breast-conserving therapy is currently considered optimal therapy of breast cancer, the disease we are trying to prevent [33]. The fallacies of proposed management based on retrogressive statistics have been considered and the need to perform clinical studies aimed at determining the best possible beneficial treatment of non-invasive breast cancer is confirmed [34].

Lobular carcinoma in situ (LCIS)

Breast cancer of this type forms in breast lobules [35]. The breast cancer has not spread outside the lobules into the breast tissue [36]. Lobular carcinoma in situ is commonly referred to as non-invasive breast cancer [37].

Ductal carcinoma in situ

It is most general type of non-invasive breast cancer, confined to the breast duct. Ductal comedocarcinoma is an example of ductal carcinoma in situ [38].

Invasive breast cancer

It occurs when abnormal cells from inside the lobules or milk ducts divide out into close proximity of breast tissue [39]. Cancer cells can travel through the breast to other areas of the body via immune system or the systemic circulation [40]. They can migrate early during development when the tumor is a minute or later when

the tumor is enormous Invasive breast cancer is most common general carcinoma in women. The areas of high risk are the affluent populations of Australia and Europe wherever 6% of women have invasive breast cancer before 75 years of age. The occurrence of breast cancer increases rapidly with advancing age [41]. Invasive breast cancer that spreads to other organs of the body is also known as metastatic breast cancer [42]. Most frequent organ to which these cells metastasize are brain, bones, lungs and liver. These cells again segregate and grow irregularly and form new cancers. New developing cells are growing in other part of the body, it is again breast cancer [43].

Infiltrating lobular carcinoma (ILC)

Infiltrating lobular carcinoma is also known as invasive lobular carcinoma. ILC begins in the milk glands (lobules) of the breast but often spreads to other parts of the body [44].

Infiltrating ductal carcinoma

Infiltrating ductal carcinoma is also known as invasive ductal carcinoma. IDC begins in the ducts of the breast milk and spreads to the duct wall, invading fatty tissues of the breast and most likely other tissues of the body [45].

Medullary carcinoma

Medullary carcinoma is a type of invasive breast cancer that creates a distinct margin normal tissue and medullary tissue [46].

Mucinous carcinoma

It is known as colloid carcinoma, mutinous carcinoma is a rare breast cancer formed by the mucus-producing cancer cells. Women with mutinous carcinoma also tend to have a better prognosis than women with other general types of invasive carcinoma [47].

Tubular carcinoma

Tubular carcinomas are a specific type of invasive breast carcinoma. Women with tubular carcinoma generally have a better prognosis than women with other general types of invasive carcinoma [48].

Inflammatory breast cancer

Inflammatory breast cancer is the type of breast enlargement (red and warm) with dimpling and/or wide ridges because of the blockage of lymph vessels or channels in the skin covering the breast by cancer cells. Although inflammatory breast cancer is rare and is immensely rapid-growing [49]. Therapy consists of careful coordination of all multidisciplinary modalities, such as radiation treatment, surgery chemotherapy and imaging. The delivery of neoadjuvant chemotherapy has given way to significant improvement in overall survival since the initial report of this issue and has fulfilled the role of locoregional therapy like radiation and surgery that is important to long-term gains in this disease [50].

Paget's disease of the breast

It is the rare form of breast cancer that generally produces noticeable alterations to the nipple of the breast [51]. Its indications are red sore rashes affecting the nipple and later on can spread to the regular skin as well. Though it looks alike with other skin diseases like eczema and psoriasis but can be distinguished because the other skin diseases tend to affect both breasts and may begin from the areola instead of the nipple of the breast whereas Paget's disease of the breast tends to affect only one breast and begins with the nipple of the breast instead of areola (breastcancercare.org.uk) Almost 1–3% of all the breast cancers are Paget's disease and can occur in both

men and women. The true theory of pathogenesis or etiology of Paget's disease of the breast is not yet understood however there are some theories favoring its pathogenesis. They have warning signs like bleeding and oozing of discharge from the nipple, flattening or inversion of nipple, lump in the breast etc. It can be diagnosed by punch biopsy. Its prognosis is favorable if it is limited within the nipple or in the breast ducts [52].

Phyllodes tumor

Phyllodes tumors are either benign or malignant [53]. Phyllodes tumors occur in the breast's connective tissues and can be treated by the removal of surgical procedure [54]. Phylloides tumors are very rare; less than 10 women die as a result of this type of breast cancer annually in the United States [55].

Triple negative breast cancer

Breast cancer is currently well-documented that is a heterogeneous disorder with distinctive sub-forms, characterized by way of their different clinico-pathological features, prognosis and therapy responses.

Triple-negative breast cancer is characterized by the lack of progesterone receptor, human epidermal growth factor receptor 2 and estrogen receptor expression [56]. This form is chiefly destructive, typically seen in premenopausal women, and accounts for 10–15% of white women's cases, with an increased incidence [57].

Pathogenesis of breast cancer

The breast is a tubulo-alveolar organ with intricate complexity embedded in an asymmetrical connective tissue [58], which undergoes a sequence of transformation from child-bearing age to senility. The alteration with each menstrual cycle and each pregnancy led us to presume the presence of precursor cells in mature tissue capable of synthesizing new duct-lobular units [59]. The normal breast architecture has a stratified epithelium surrounded by a basement membrane and embedded in a template of blood vessels, lymphatic and stromal cells [60]. In the normal breast, the stratified epithelium made up of two distinct populations of cells, myoepithelial and epithelial cells, which can be identified using immunohistochemical staining with antibodies directed against myosin and CK, respectively. It has been theorized that the development of cellular heterogeneity in breast pathoses relies on the initial developmental series of the normal breast. This heterogenicity of the breast cancer could occur from the neoplastic transformation of either epithelial or myoepithelial cell, or even from a stem cell capable of becoming a myoepithelial or an epithelial cell [61]. Based on the oncology of breast cancer, neoplastic cells are different from normal body cells. There is limited growth promotion and regulation in normal body tissues that maintain the structure and function of tissues as usual. But cancer cells cause chronic and prolonged growth without any stimulus [62]. Cancer cells bypass the growth suppressor genes [63]. Breast cancer is a cancerous condition that starts in the breast tissue. Similar to other cancerous tumors, there are many causes that contribute to the likelihood of developing breast cancer. Damage to the deoxyribonucleic acid (DNA) and genetic mutation can lead to breast cancer have been linked with the exposure of estrogen. Some of the patients inherit error in the deoxyribonucleic acid (DNA) and genes such as the P53, BRCA1 and BRCA2 and others. The patients whose families have a history of breast or ovarian cancer have chance to develop breast cancer [64]. The neoplastic cells take high potential to grow and develop into a huge tumor [65]. The immune system generally attempts to identify cancer cells and cells with damaged deoxyribonucleic acid (DNA) and destroy them. Breast cancer could be a result of failure of such a beneficial immune defense and vigilance. Breast cancer may develop because of a combination of genetic and environmental components. RAS/MEK/ERK signaling pathway and PI3K/AKT pathway protect normal cells against cell suicide. When there is mutation in genes that are responsible for encoding of such protective mechanisms, the cells lose the capability of committing suicide if they are no longer needed leading to cancer development. These mutations were found to be experimentally linked with exposure to estrogen [66]. Deformity of growth factor signaling was suggested to promote growth of malignant cells. Over expression of leptinin breast adipose tissue increases

cell proliferation and cancer [67]. These are many growth factors signaling and other factors that interact between stromal cells and epithelial cells. Disruption of these can lead to onset of breast cancer. In cancer cells, telomerase enzyme wards off the shortening of chromosomes and enables the maximal replication of cells [68]. Tumor cells obtain their nutrition and oxygen supply through angiogenesis [69]. Cancer cells invade their boundaries and are able to enter the blood, lymphoid tissues and other tissues of the body to form a secondary tumor [70].

Etiological factors and risk factors of breast carcinoma

Breast cancer is the most prevalent cause of death among British women aged 40–55 years. Single women are more likely to develop breast cancer compared to married women [71, 72]. The breast is an estrogen-sensitive organ. Numerous women who have taken birth control pills or estrogen replacement have discovered that the drugs cause their breasts to enlarge and become tender to the touch. Activity of this drug, along with the typical western high fat, low fiber diet, which over-stimulates the breast tissue, may be a stimulus to breast cancer. Breast cancer incidence is more common in women over 50 years and 2 cases per 1000 are seen in this age group. Epidemiological studies have also proposed that such women who have lots of children have less risk of breast cancer compared with those women who give few children. Breast cancer incidence is 10.04% among total cancers and, most often is seen in 40–50 years old women. Iranian women's mean age for breast cancer is 48 years [73]. An Iranian women clinic pathological characteristic association with breast cancer subtypes has been established [74]. Breast cancer predominantly presents in obese women [75]. Depression is predominantly seen in women with breast cancer [76]. Andsoy et al. [77] presented a study to assess knowledge of colorectal, cervical and breast cancer. For this purpose 226 working nurses were screened. It is quite surprising that some epidemiological researches have asserted that women who deliver their child prior to reaching the age of 20 years are found to have lower risk of breast cancer compared to those women who have never delivered any child or have delivered their first child at an age beyond 30 years. The risk accelerates with age in premenopausal and decelerates in post-menopausal life. Breast feeding reduces the risk of breast cancer

[78]. Menopause caused by surgical removal of ovaries (oophorectomy) reduces the risk [79]. The presence of some types of benign tumors in breast raises the risk of malignancy [80]. The ovaries cease to produce the female hormones after menopause begins, but in obese women the body fat can supply the estrogen since it is able to synthesize it. This growth of hormone production appears to elevate the risk of breast cancer in post menopausal obese women. Vitamin D deficiency and sun exposure deficiency are known to be the significant etiology of breast cancer [81]. It is more prevalent in females than males [82]. Breast cancer risk grows with age but seldom seen before 20 years of age [83]. One breast carcinoma can elevate the risk to four times in the other breast. Though the patients with a history of ovarian, endometrial or colon cancer have 1–2 fold elevated risk to develop carcinoma of the breast [84]. A woman who has experienced breast cancer has an increased risk of developing breast cancer in the other breast [85]. Minimal involvement of the gene is identified in the etiology of breast cancer. BRCA-1 (breast cancer susceptibility gene) is regarded to be responsible for 5–10% of the breast cancer that is inherited from either the father or the mother to subsequent generations. The research shows that the proper environmental conditions are necessary for the expression of cancer promoting gene. Some families have been found with a genetically increased prevalence of early onset breast cancer. If the female's family has had a particular type of cancer, then female can have an increased risk of danger of breast cancer [86]. The risk is highest if the cancer patient in the family was diagnosed with breast cancer at an early age, or if the individual had cancer in both breasts, or if the female belongs to a close family. First-degree relatives like mother, sister and daughter are primarily important in threat estimation. Many second-degree relatives like an aunt and grandmother with breast cancer can also increase the threat. Male breast cancer increases the risk for all close female relatives. Females with a positive family history of breast carcinoma have 2–4 times higher chance of developing the cancer, particularly the female carriers of BRCA1 or BRCA2 genes have the

substantial likelihood of developing carcinoma of breast [87]. Breast cancer is present in both male and female; although, the incidence is greater in female compared to male. In general, females are at 100-fold higher risk of breast cancer than male [88]. Early menarche, nulli parity, age at pregnancy more than 30 years, oral contraceptives or hormone replacement therapy all these conditions can cause increase in the risk of breast cancer [83]. Steroid hormones consist of androgens, progesterone and estrogen, which are members of a group of structurally related hormones called sex hormones secreted into the bloodstream by the adrenal glands and gonads. They are formed from one general precursor molecule, cholesterol via an enzyme-catalyzed reaction to produce a wide variety of hormones for multiple target organs and tissues [89]. This process is nicely regulated and the release of these hormones into systemic circulation. These hormones enter the target cells by passing across the plasma membrane and bind to certain receptors known as steroid hormone receptors to become active [90]. Oestrogens play significant actions on differentiation, growth and functioning of a number of tissues such as urogenital system of man and woman, cardiovascular system, brain, uterus and breast [89]. Consistent with this, Kato et al. [91], stated that the development of reproductive organ cancer such as prostate and breast cancer often results due to the androgens, progesterone and estrogen, which have multiple biological activities in normal and abnormal cells. The research suggests that the differentiation of normal and abnormal epithelial cells of the breast can be regulated by the stromal cells of the breast and can secrete growth factors following stimulation by the endogenous hormones. There is an enzyme called aromatase present in adipose tissues, which synthesizes estradiol from the precursor molecule, cholesterol. The fat cells are present in excess number in breast of older women; thus, the content of estradiol is greater in breast tissue of post- menopausal woman compared to their plasma content [92]. This is very likely to cause the growing incidence of breast cancer in older female and helps the role of steroid hormones in pathogenesis of breast cancer. Benign tumors and proliferative lesions with or without atypia may enhance the risk of breast cancer [85]. Breast cancer has been associated with high intake of dietary fat and low intake of certain nutrients for numerous years [93]. Animal fat activates colonal bacteria to produce estrogen from dietary cholesterol, thereby elevating the body's estrogen level. The body fat also participates in oestrone synthesis, a form of estrogen. Obesity, elevated consumption of fat, radiation therapy [94]. There is growing evidence that selected environmental pollutants play a role in estrogenic activity and perhaps in accounting for the incidence of breast disorders in the industrialized world. Alcohol intake is associated with risk of breast cancer. This correlation was perceived to be secondary to the understanding that alcohol consumption increases blood levels of hormones [95].

BRCA1 and BRCA2

These are two genes that have been identified to carry the strong association with breast cancer. Both arise to possess similar biological functions like DNA damage repair and, in their variant form, they increase the risk of breast cancer and other ovarian cancers. The superior information available till now is derived from a combined study of 22 studies, 11 of which determined that the risk of breast cancer is 65% at age 70 in women who have inherited a BRCA1 gene and 45% in such women who are carriers of BRCA2 genes. The incidence of breast cancer among carriers of these genes is 10–30 times greater than in those women who have no inherited gene mutations. Despite the significant increase in breast cancer risk associated with BRCA1 and BRCA2 genes, they account for about 5% of all breast cancers, since only 1 in 1000 women have inherited one of them. There are a number of tribal Subgroups where BRCA1 and BRCA2 genes are more likely to be inborn (e.g. around 1% of women who belong to Ashkenazi Jewish origin have inherited elevated risk BRCA1 or BRCA2 genes; similar variants are also well known in women who belong to Iceland and other Scandinavian nations). Personal risk indicator as a result of inherited testing for BRCA1 and BRCA2 is still a challenging ordeal. Near 2000 variants have been identified within the two genes (BRCA1 and BRCA2) and, for many, it is still not known whether they increase incidence of breast cancer or not. The location of the variant within the gene is one possible indication that variants within some regions of the genes may create greater risk of breast cancer than

others [96, 97]. Even though all females who acquire a BRCA1 or BRCA2 variant do not essentially cause breast cancer, it is uncertain what other determinants such as genetic or environmental persuade the risk of breast. There is also promising data that determinants for breast cancer might perform in a different way for carriers of BRCA1 or BRCA2 variants than for females lacking hereditary vulnerability because of these genes [98]. Literature review further suggests that other high-risk genes apart from BRCA1 and BRCA2 potentially increase the risk of breast cancer, predominantly in young women.

Mortality

Fifth most frequent cause of death due to cancer is breast cancer. The death and age-standardized prevalence of breast cancer is greater in the United States than globally. Seventeen percent of cases of diseases arise in Poland because of cancer and 14% mortality arises because of cancerous changes. Global mortality because of breast cancer estimated in 2004 was 519,000 [99]. In the USA alone, about 1,208,000 cases of cancer are reported annually and that about 538,000 individuals succumb to the prior expression of this disease condition, accounting for roughly one fifth of the total yearly deaths from any cause [74].

Stages of breast cancer

As per the report of breast cancer.org Stages of the breast cancer depends on the size and type of tumor and how deeply the tumor cells have invaded in the breast tissues [100]. While stage 0 is for the non invasive and stage 4 is for the invasive type of tumor. Descriptions of those tumor stages are:

Stage 0

This is the non invasive stage of the tumor, which shows that cancerous and non cancerous cells are within the limits of that part of the breast in which the tumor starts developing and no proof of their invasion in the tissues surrounding that part, the example of this tumor stage is ductal cell carcinoma in situ (DCIS) [101].

Stage 1

This phase defines as the breast invasive carcinoma and microscopic invasion can occur in this phase. It has two types that are 1A and 1B stage. 1A defines the tumor which is up to 2 cm and none of the lymph nodes are involved in it but stage 1B defines that few small numbers of cancer cells more than 0.2 mm founds in lymph node [102].

Stage 2

Stage 2 also has two types 2A and 2B. Stage 2A mentions that the tumor is present in axillary lymph nodes or in sentinel lymph nodes but no tumor detected in breast. The tumor can be small or big but not exceeding 5 cm. But stage 2B mentions that the tumor may be more than 5 cm but can't extend to the axillary lymph nodes [103].

Stage 3

It is broken down into three sub categories which are 3A, 3B and 3C. Among which stage 3A mentions that there is no tumor in breast but may be present in 4–9 axillary lymph nodes or in sentinel lymph nodes whereas stage 3B mentions that the tumor may be of any size but have resulted in swelling or ulcer on the skin of the breast and may have involved as far as 9 axillary lymph nodes or to sentinel lymph nodes stage 3B may be regarded as inflammatory breast cancer which involves red, warm and swollen breast skin. But stage 3C explains the spread of cancer till 10 or above 10 axillary lymph nodes and it has also involved the lymph nodes above and below the clavicle [104].

Stage 4

This is the metastatic and advanced stage of cancer and this stage explains the spread to other parts of the body that is lungs, bones, liver brain etc [105].

Diagnosis

History and physical examination

Clinical history of breast cancer patients is designed to explore cancer danger and to show the presence or absence of signs consistent with breast disease [106].

It should include age at menarche, menopausal status, previous pregnancies and use of hormone replacement therapy following menopause or use of oral contraceptives. Personal history and family history should be conducted in detail. Personal history encompasses age of diagnosis of breast cancer, prior breast biopsies and other cancer treatment involving radiations. Family history encompasses history of ovarian cancer and breast cancer in first degree relatives. Patents are to be evaluated for specific findings like pain in breast, weight loss, bone pain, fatigue and nipple discharge [107]. Physical examination involves observation of breasts, neck and collarbone region, and armpit (axillae) by clinicians [108]. Breasts are checked for any deformities like lumps or any other sign of breast cancer. Lymph nodes are also checked that are typically enlarged in breast cancer patients.

Self-examination

Utility of the breast self-examination is controversial due to the fact that benefit in terms of lower deaths has not been found [109]. Most doctors teach women to perform monthly BSE in order to become familiar with their normal structure and empower them in relation to their own medical care [110]. Women are instructed for self examination of the breast cancer. On self examination, women can detect abnormalities in size and shape of breast [111–113]. Alipour et al. [114] carried out a study to examine the SMS based and paper based paper learner's satisfaction and learning effect. Printouts and text messages of facts of breast cancer and tests of breast cancer were provided by gynecologists. Physicians discovered greater motivation and improved effects in the SMS group compared to the printed material group. Sreedharan et al. carried out a study in United Arab States hospitals. Self administered structured questionnaire was utilized to examine the practices of self examination and knowledge. Acceptable findings were obtained from this study [115]. Ozkan et al. [116] examined the knowledge level concerning self examination of the breast cancer among 113 nursing and midwifery students. These studies have identified that continuous education programme on breast cancer can increase the awareness among the population. Ceber et al. [117] carried out research on breast self-examination and health perceptions of Turkish women and declared that physical diseases and premature death can be avoided through early diagnosis of breast cancer. He also declared that among every seven patients suffering from breast cancer, one is diagnosed in time. Beydag and Karaoglan [118] examined awareness regarding breast self examination among 1st and 4th years students and made a conclusion that 4th years students are more knowledgeable about the breast examination compared to the 1st years students.

Ultrasound breast imaging

There are many studies behind the use of adjunctive screening ultrasound in high risk women with dense breast tissue, which shows a considerable but known rate of false positives [119, 120]. There is no randomized clinical trial that has been performed for investigation of effect of screening ultrasonography on mortality rates of breast cancer. Whole breast ultrasound could allow the Physicians to show for breast tumors not detected by time-tested mammography, especially in dense breasts where the sensitivity of mammography is lower [121]. Breast imaging by ultrasound demonstrates tumor size and location whether it is fluid-filled or solid and must be

biopsied to exclude cancer. This test is rapidly evolving as a standard technique for the diagnosis of lumps in young women [122, 123].

Nuclear medicine

It is a form of molecular imaging wherever the radioactive agent (radiopharmaceutical) is administered to a patient and radiation emitted by the radiopharmaceutical is observed by sensitive emission detectors such as gamma cameras and PET detectors and gamma Cameras placed outside the patient's body. Integration of CT and gamma camera and integration of CT and PET is a primary advancement in increasing recognition and proximity of disease.

Single photon emission computerised tomography (SPECT)

This process involves single photon radionuclides such as gallium-67, iodine-131 and technicium-99 m that emit gamma rays. It is an effective scan and is accurate for organ of interest. It can also be used to the whole body, is relatively safe in terms of radiation amount and is excellent in detection of initial and metastatic cancers. Iodine-131 is simultaneous diagnostic to and therapeutic for cancer of the thyroid [124].

Positron emission tomography (PET/CT)

In terms of radiation quantity, PET/CT is also relatively safe and employs positron emitting radionuclides such as oxygen-15, flouoride-18 and carbon-11. The most commonly used tracer in positron emission tomography is a radioactive form of glucose like [18F]fluoro-2-deoxy-d-glucose. Cancer cells that are growing have increased metabolic needs such as developing cancer cells, which exhibit increased accumulation of the tracer and reflect on the scan. With the combination of CT and PET, valuable information about many situations involving the various organs of the body is just mapped. PET/CT is highly sensitive and specific for predicting occult and various regions of loco-regional lymph nodal spread and/or distant metastases not apparent by conventional imaging, thus changing staging in up to 25% of the patients. This process is utilized for the planning of management by outlining spread of basic disease. It is also utilized in re-staging following relapse of ailment after management and treatment follow up [125].

Tumor markers

Porika et al. [126] added that tumor markers need to be assessed in all phases of the breast cancer including prediction of metastasis, treatment, diagnosis, and screening. Thirteen verities of breast cancer tumor markers are quantified, six of 13 are new to the guideline. The various types exhibited evidence of clinical application and are recommended for use in practice [127]. Of particular importance is the relative independence of the markers from other available markers to which they provided evidence in order to avoid the gratuitous cost and expense of redundancy [128]. In addition, it is worth noticing that the doctor should be mindful of the limitations in both specificity and sensitivity of each marker so since not to over- or under-estimate the prognostic value of a few tests. On these reservations to intelligence, trial submission of tissue, germ-line and soluble tumor markers can restore medical care of individuals at risk for and with breast cancer.

Ca 15-3

It may be used for patient monitoring in breast cancer. Elevated blood levels are observed in <10% of patients at the onset of breast cancer and in about 70% of patients with advanced stage breast cancer. The levels of CA 15-3 generally decline following successful treatment. But CA 15-3 can also be elevated in other cancers and in some non-cancerous conditions like hepatitis and benign breast disease.

Ca 27.29

It is yet another marker for patient monitoring with breast cancer. This test does not appear to be any better to detect early or late stage of breast cancer. This tumor marker occurs in other cancers and in some non-cancerous diseases.

Estrogen and progesterone receptors

For the diagnosis of breast cancer, tissues of breast cancer are examined for estrogen and progesterone receptors as well as HER2 antigen. The tests provide information about the aggressiveness of cancer and sensitivity of some drugs employed for the treatment of breast cancer.

Immunohistochemistry

Immunohistochemistry (IHC) has become a very important part of pathology. While eosin and hematoxylin stain is the main basis for diagnostic breast pathology, Immunohistochemistry stains provide useful and sometimes extremely significant information. In addition, considering the role of hormonal treatment in hormone receptor–positive breast cancers, as well as the availability of targeted chemotherapeutic agents to HER2-positive patients, Immunohistochemistry information reflects an essential aspect of workups. Precise application of Immunohistochemistry stains in conjunction with E & H test helps determine primarily diagnostic issues faced by clinicians in their day-to-day practice. Clinicians must be well-acquainted to apply the each immunostain and its limitations to avoid misinterpretation. Immunohistochemistry stains helps differential diagnosis of problematic epithelial diseases of the breast. They are to be used selectively and judiciously and their outcomes need to be interpreted with the differential diagnoses in mind and keeping in view the possible drawback [129].

MRI and breast cancer

Mammography has been thought to be the proper screening technique for breast cancer detection for decades [130] but can't differentiate between the solid and cystic masses and can miss 10–15% of the cases but MRI gives better results and definite advantage to the women who are getting breast cancer due to the BRCA1 and BRAC2 gene mutation and are also having the axillary lymph adenopathy [131].

Breast biopsy

Breast biopsy is the plainest best method of breast cancer diagnosis [132]. There are many various types of breast biopsies. In order to increase diagnostic accuracy and eliminate as many false negative results as possible, breast imaging, clinical breast examination and biopsy are executed at the same time (triple test).

Fine needle aspiration

A fine prick is used to obtain cells from the abnormal region or a breast mass [133]. Ultrasound may be used to help guide the prick. A limited anesthetic may be used to numb the area where the prick is to be inserted [134].

Core biopsy

A larger prickle is to remove a portion of tissue (a core) from the abnormal region or lump of breast [135]. It is usually done under limited anesthetic, hence breast is insensitive, whereas patient could feel little pain or discomfort at the time the anesthetic is administered [136]. Ultrasound, MRI and mammogram can be utilized to guide the prickle during the period of core biopsy [137].

Vacuum assisted stereotactic core biopsy

In core biopsy, various small pieces of tissue are obtained through single small cut in the skin with a prickle and a suction device [138]. This is done under local anaesthetic. MRI, ultrasound or mammogram can be used to guide the prickle into place. The patient can feel slight discomfort during this procedure [139].

Surgical biopsy

If the abnormal location is too small to be biopsied with another method or the result of the biopsy is not evident, a surgical biopsy is performed. Before doing the biopsy, a guide wire might be inserted into the breast to guide the medical doctor to the abnormal tissue. Local anesthetic might be utilized and MRI, ultrasound and mammogram can be utilized to guide the wire to position. The biopsy is then performed under a general anesthetic. Minimal tissue near breast tissue and lump are removed, along with the wire [140, 141].

Digital mammography

It assists in detecting lumps in thick tissue. The picture can also be stored and sent to another radiologist for a second opinion easily [142–144]. Tarhan et al. [12] explained mammography can produce false negative and false positive results in individuals with thick breast tissues. Kanaga et al. [145] explained the 19% practice of mammography is in Malaysian women compared to another study that was 10.5%. Lack of health insurance coverage, low income and embracement were the main barriers to mammography as mentioned in earlier studies. Mammography is used as the gold standard screening to detect breast cancer early [146] but if there is a scarcity of resources in some regions in breast health awareness program must be encouraged for the early detection of breast cancers and the personnel must also receives the training of clinical breast examination so that the patient gets diagnosed at an earlier stage particularly in those regions where mammography is not available [147].

PEM and MRI in breast cancer patients

Thus both the magnetic resonance imaging and positron emission mammography have shown breast cancer detection sensitivity, yet hormone replacement therapy, post menopausal status and breast density has no effect on PEM and MRI sensitivity. Positron emission mammography may serve as a substitute of MRI in those patients who don't wish to undergo an MRI for various reasons including time concerns, financial constraints, lack of interest, claustrophobia (fear of being confined in such small space) [148]. Both share the same sensitivity to detect cancerous lesions understanding invasive and ductal carcinoma in SITU [149].

Treatment

In breast cancer management, a goal is to maintain quality of life with increased life expectancy. Inhibition of estrogen production has been suggested by the use of bioflavonoids [150]. Good communication between physicians and patients helps to enhance clinical outcome. Effective communication between physicians and patients was effective, as reported by Oshima et al. [151]. A Japanese study suggests that this communication assists the patients in managing adverse effects. Doctor-patient communication improves the quality of life of breast cancer patients [152]. Earlier research has indicated that lower exposure from radiations, greater family monthly income, greater years since diagnosis, greater education, earlier stage cancer and younger age were significantly associated with greater quality of life (QOL) in breast cancer patients [153]. Breast cancer is less frequent in breast feeding women, but the protective effect of this factor is not quite examined [154]. Cancer is a killer disease of humankind across all nations. Vinblastine and vincristine was launched in 1961 as anti cancer agents. CIPLA has enhanced vinblastine and vincristine isolation process in the World [155], and India is shipping the alkaloids to European nations and the market is continuously growing. The primary modes of cancer treatment in human beings are surgery, radiation and chemotherapeutic drugs. The drugs are able to

provide symptomatic relief on a temporary basis, prolongation of life and even sometimes cure the disease. Dozens of hundreds of chemical drugs of well-defined classes of cancer chemotherapeutic agents have been prepared [156]. Activity of these compounds relies on their ability for biological alkylation. The dose of such alkylating agents required for effect was roughly equivalent to the toxic dose. Multi-targeted treatment would be better, as the rate of cancer recurrence is high and it leads to death by metastasis. Deng et al. [157] have stated that Pemetrexed and Lobaplatin is administered in metastatic breast cancer. Huang and Cao [158] have stated that cantharidin sodium injection is effective for the treatment of breast cancer. Cantharidinate sodium injection is of herbal origin and is made in China for the treatment of breast cancer. Breast cancer management plans vary based on the stage of the cancer—its mass, location, whether it has spread to other organs in the body and the patient's physical status. Current management for breast cancer comprises targeted therapies, hormone treatment, radiation and surgery.

Psychological adaptation to breast cancer

Breast cancer is very prevalent and very distressful experience for many females every year in developing and developed worlds [159]. Psychological studies have provided a picture of the affective and community effect of breast cancer on females' lives, and of predictors of improved versus poorer change. Psychosocial mediations have proved useful in alleviating patients' mourning and enhancing their quality of life. Recent research also suggests that psychological factors may be related to potentially important biological disease associated processes. Further, to providing an indication of the psychological factors in breast cancer, research in this area has provided a basis for subsequent studies on adjustment to health-related nervous tension in general [160].

Surgery

This is the primary management approach for patients whose breast cancer has not spread to other parts of the body and also an option for additional complicated stages of the disease [161–163]. Types of breast cancer surgery range in the amount of tissue removed along with the cancer; this will rely on the characteristics of the cancer, whether it has spread, and the patient's special emotions. Few of the most common types of surgery are:

Lumpectomy (breast conserving surgery)

Certain patients with breast cancer receive some form of surgery [164]. American cancer society states that lumpectomy or partial mastectomy is the removal of the portion of the breast where the malignant tumor is situated along with a few healthy tissues and related lymph nodes and leaving the bulk of the breast as intact as possible [165]. This procedure typically involves in women who want to have their first stage of cancerous attack, but the patient also needs another form of treatment like radiation therapy, chemotherapy or hormone replacement therapy in addition to this operation. The majority of surgeons and patients also want lumpectomy first then removing the whole breast, especially when the patient does not care about losing her breast [166]. But the side effects of lumpectomy include tenderness, transient inflammation, sclerosis and altered contour of the breast, etc [167].

Mastectomy

Mastectomy is performed to reduce the risk of occurrence of breast cancer [168]. Bilateral prophylactic mastectomy reduces the risk of occurrence of breast cancer but does not prevent development of cancer at all [169]. Aromatase and tamoxifen reduces the risk of contra-lateral breast cancer and it is more effective than contra lateral prophylactic mastectomy [170]. Mastectomy is the best approach to addressing a case of already diffused breast cancer, for which lumpectomy proved too indecisive. However, loss of breast tissue results in a sense of asexuality and loss of self-image and resultant depression in the majority of women [171].
Reconstructive surgery

Women undergoing a mastectomy could just as well undergo breast renovation, either immediate or delayed reconstruction. It is done to improve the appearance of the breast after tumor surgery. All women undergoing mastectomy should be offered the opportunity to discuss reconstructive surgical treatment [172]. Mastectomy is a relatively straightforward surgical procedure that usually necessitates hospital stay for 1–2 days. Lack of the breast mass alters the patient's special appearance and may make wearing some types of clothing challenging. Use of an outside prosthesis to address these issues may be uncomfortable and irritating, especially for women with large breasts. Although, the most paramount problem of mastectomy is the psychosocial impact of the bodily and aesthetic deformation, which may include nervousness, depression, and negative effects on figure of the body and on sexual activity [173]. Breast reconstruction is often asked for by women with breast cancer who are not able for breast-conserving therapy and women with a higher hereditary risk for breast cancer. Current breast reconstruction techniques are disparate and may involve the use of prosthetic implant or autologous tissue flap, or both. Irrespective of the technique used, cancer may recur in the reconstructed breast; further, in autologous tissue flaps reconstructed breasts, minimal complexity like fat necrosis may occur. Studies suggest that breast reconstruction reestablishes body representation, demonstrates vigor, femaleness, and sexuality; and positively affects the patient's sense of comfort and quality of life [174].

Ovarian ablation as adjuvant treatment of breast cancer

Ovarian ablation has been used as therapy of breast cancer [175]. Various methods of ovarian ablation include radiation induced ablation, surgical ovary removal and long-term use of luteinizing hormone-releasing hormone (LHRH) analogs. Moreover, some suggestions are there that cytotoxic chemotherapy may act by causing ovarian ablation in premenopausal women with breast cancer. Among the numerous case series and clinical trials of ovarian ablation that were performed in the previous era, many have been riddled with methodologic flaws. Meta-analysis of randomized clinical trials documents a landmark improvement in overall survival and disease-free survival for women whose ovarian ablation were done as adjuvant treatment versus those women who did not. Literature review shows that ovarian ablation can be used an alternative treatment for breast cancer [176].

Role of estrogen and progesterone receptors in the treatment of breast cancer

The estrogen receptor test has become standard practice in the management of advanced breast cancer [177]. Tumors which are estrogen receptor negative respond infrequently to endocrine therapy, whereas improvement rates of 50–60% occur in estrogen receptor positive tumors. Newer studies indicate that the estrogen receptor status of the primary cancer is an even better interpreter of the endocrine dependency of metastatic cancers at the time of clinical decline. Also, the lack of estrogen receptor in the initial cancer is a notable self-regulating predictive indicator of increased incidence of recurrence and decreased survival. Quantitative assessment of estrogen receptor and an analysis for progesterone receptor are two processes for increasing the accuracy of selection or rejection of individuals for hormonal therapy; cancers with a high quantitative estrogen receptor level or those having a positive progesterone receptor exhibit maximum response. Initial studies prove that the presence of progesterone receptor may be a better marker for tumor hormone dependence than qualitative estrogen receptor [178].

Anti estrogen treatment

It can be employed in such cancers which are hormone-sensitive and the tumor contains hormone receptors like estrogen receptors. Clarke et al. [179] reported that the most frequent type of medication that is utilized in breast cancer is anti estrogen and those agents which are (tamoxifen, raloxifene, toremifene etc). Tamoxifen prevents the hormone oestrogen from coming inside cells of the breast cancer. This mechanism prevents the development of the breast cancer cells. Tamoxifen may be recommended to treat female of any age. But tamoxifen is regarded as the drug of choice in women who have positive estrogen receptor breast carcinoma. Tamoxifen is a selective

estrogen receptor modulator (SERMS) and exerts estrogen-like action in other areas of the body like uterus. But it proves anti estrogenic activities of breast tissue and has a competition with estrogen for the attachment to the estrogen receptors within the breast [180]. If we have to talk regarding the toxic activities of anti estrogen therapy, relatively there is least toxicity present in it in comparison to other cytotoxic agents [181]. Though, some patients withdraw the treatment midway before finishing the course of drug due to side effects like hot flushes, gastro intestinal issues and vaginitis etc. However, the indications for stopping the antiestrogen therapy are adeno carcinoma, sarcoma and thrombo embolic diseases etc. Anyway, the American society of clinical oncology also recommends Tamoxifen as adjuvant therapy of choice for Estrogen positive breast carcinoma patients [182]. Conversely Fulvestrant; Faslodex has completely anti estrogenic activity and is studied as estrogen antagonist it shows anti neo plastic activities in breast tissues without showing any beneficial effect on uterus and bones, which might result in some side effects if used for a prolonged duration of time like osteoporosis [183]. Tamoxifen and raloxifene are selective estrogen receptor modulators (SERMs), a class of drug that selectively prevents or induces oestrogen-like action in various tissues, influencing the estrogen receptors [184]. Tamoxifen finds its oestrogen antagonist effect in various tissues like uterus, liver, bone and breast [185]. It was employed as adjuvant therapy in estrogen receptor positive patients and tamoxifen was approved by the United States Food and Drug Administration (FDA) in 1998 for the prevention of breast cancer in women at high risk [186]. This decision was made following the result of an experiment conducted by the United States National Cancer Institute that was halted early as an intervening trial revealed that tamoxifen reduced breast cancer incidence by about one half [187, 188]. Four large prospective studies have examined the value of tamoxifen versus placebo for breast cancer risk reduction in women at higher risk of breast cancer [189]. A summary of these trials revealed a 38% overall reduction in the incidence of breast cancer for women at high risk of breast cancer who took tamoxifen for the duration of 5 years and also showed that tamoxifen prevents only estrogen receptor positive breast cancers (RR ~ 50%) with no effect on estrogen receptor negative breast cancer [190]. Many of the side effects have been severe in females taking tamoxifen including venous thrombosis, cataract, endometrial cancer, menstrual abnormality and hot flushes. The activity of decreasing risk for severe effects of tamoxifen extends beyond the intensive management period of 5 years, and continues for at least 10 years, while most of the side effects do not continue beyond behind the severe management period of 5 years [191]. Raloxifene, has also been found to reduce risk of breast cancer, but appears to cause some unfavorable effects [192]. Throughout the previous times, clinical trials conducted to explore the effectiveness of raloxifen on fracture and osteoporosis, indicated a 44–76% risk reduction of the occurrence of breast cancer in the patients treated with raloxifen compared to the control group [193]. A randomized clinical trial of Tamoxifen and Raloxifen was to be undertaken for comparing the efficacies of tamoxifen and raloxifen on postmenopausal women with an improved 5-year risk of breast cancer as predicted by the Gail model [194, 189]. The trial showed that raloxifen was equivalent to the tamoxifen in reducing the risk of invasive breast cancer and was associated with a slight risk of cataract and thromboembolism than tamoxifen. In 2007, about 10 years after tamoxifen was endorsed, the FDA approved raloxifen for the prevention of breast cancer in postmenopausal women with osteoporosis and for postmenopausal women at higher risk for breast cancer. Tamoxifen is used in Australia to treat breast cancer and osteoporosis.

Aromatase inhibitors

These are complex for reduction of oestrogen synthesis by inhibiting aromatase, the enzyme complex responsible for the final step in estrogen synthesis [195]. Third-generation aromatase inhibitors such as letrozole, exemastane and anastrozole are in current use [196]. Randomized clinical trial performed for study of these drugs in treating breast cancer has shown that these compounds hold a superb efficacy in treating women with advanced disease. Clinical research established that women treated with aromatase inhibitors had a higher contra lateral breast cancer risk reduction compared to women treated with tamoxifen [131].

Radiation therapy

It is beneficial in minimizing the need for mastectomies. Both a lumpectomy coupled with radiation therapy are being increasingly utilized in place of a mastectomy in the initial stages of breast cancer [197]. A study was conducted in India. For the purpose of this study 135 women were chosen, and most of them had already been subjected to mastectomy. At analysis time, no local recurrence occurred after hypo fractioned radiation therapy and metastatic disease occurred in only four patients [198]. Zhou et al. [199] also described that radiation therapy is effective in early breast cancer patients. This study involved 143 women who received either routine or intra operative radiation therapy following breast conserving surgery. At 54 months of follow-up, there was loco-regional control of the tumor. Radiation therapy kills cancer cells with high-energy rays. This therapy targets only the treated cells. Radiation therapy use may be performed following breast cancer surgery to kill the remaining cells in the chest cavity.

Brachytherapy

It is a type of radiotherapy [200]. It could be identified as accelerated partial breast irradiation. It targets radiation only to the vicinity around the area where the cancer was. This could instead of the need to treat the entire breast with radiation. It also reduces the number of management sessions [201].

Chemotherapy

The method of killing cancer cells with the help of some medicines is called chemotherapy [202, 203]. It can be administered in both cases, pre- or post-surgery, depending on the patient's condition. According to the American cancer society the drugs included in chemotherapy are Docetaxel, Paclitaxel, Platinum drugs (cisplatin, carboplatin), Vinorelbine (Navelbine), Capecitabine (Xeloda), Liposomal doxorubicin (Doxil), Cyclophosphamide (Cytoxan), Carboplatin (Paraplatin) etc [204]. But it has several side effects [205]. Secondary or metastatic breast can is hard to cure but it may be controlled and sometimes for different years [206]. Chemotherapy can be given to control metastatic breast cancer to slow down or reduce its growth. It can be given also to reduce some symptoms. Other therapeutic option can be started before or in addition to chemotherapy.

Taxol

Taxol is being clinically used to treat ovarian cancers and is being tested clinically against metastatic breast cancers [207]. It could also be of potential value against lung, head and neck cancers. Taxotere is a side chain taxol analogue, which has also been made by semi synthesis from 10-deacetyl-baccatin III [208]. It is more water soluble, and is currently under clinical testing against ovarian, and breast cancers. It may be employed in those in whom resistance to cisplatin has been noted [209]. Anthracyclines

Anthracycline are widely used in the treatment of breast cancer [210]. They interfere with enzymes related to the copying of DNA, which is what the cells need in order to separate and form new cells. Epirubicin and doxorubicin are the most widely used drugs in breast cancers. There is evidence that anthracyclines work better than many other chemotherapy drugs [211]. Despite these, they have side effects like damage to the heart and hair loss [212, 213]. Before initiating medicines, patient should discuss with clinician any possible side effects of drugs administered and how these medications may impact the quality of life.

Thermochemotherapy

Medifocus heat treatment along with chemotherapy improved the reduction of median cancer within the thermochemotherapy group to 88.4%, as opposed to 58.8% shrinkage of median cancer for chemotherapy alone.

For the thermo-chemotherapy management group, about 80% of breast cancers saw a reduction in cancer size of 80% or greater, as opposed to just 20% for the chemotherapy-alone [214].

Complementary therapies

Women with breast cancer sometimes want to employ complementary treatments in addition to their medical treatment [215]. Such treatments are commonly not researched in randomized clinical trials [216]. Certain female feel that they have improved by means of a variety of these treatments [217]. Vitamins, nutritional supplements, yoga, meditation, visualization, traditional medicines and acupuncture are all part of complementary treatments.

Medicinal plants

Medicinal plants

Screening of plant extracts for anticancer activity started in 1961 by National cancer institute in the USA, and up to 1981 (20 years) about 1,14,045 plants had been screened of which only 3.4% (representing about 3400 different species) have been observed to be active in one or more biological systems.

Ganoderma lucidum (Polyporaceae)

It has ganoderic acid, ganoderic acid G, ergosta, ergosterol peroxide ganoderic acid G, ergosta, ergosterol peroxide, methyl ganoderate A, B, ganoderic acid C2. It is an anticancer [218]. Jiang et al. [219] reported that the Ganoderma lucidum inhibits growth of breast cancer cells by inhibiting Akt/NF-kappa B signaling. It is utilized for cancer cell treatment. It inhibits the transcription factor NF-kappa B and inhibits the invasion activity of breast cancer cells. The precise mechanism for cancer cell inhibition is unknown. The study revealed that the growth of breast cancer MDA-MB-231 cells is inhibited and Akt/NF-kappa B signaling is inhibited. Phosphorylation of Akt at Ser473 is inhibited by this plant and expression of Akt is inhibited, consequently NFkappa B activity in MDA-MB-231 cells is inhibited.

Momordica charantia *(Cucurbitaceae)*

The parts used are fruits, leaves and seeds. It contains glucoside, albuminoids, fatty acids, non polar lipid, linolinic acid, palmitic acid, myrtenol, hexenol, benzyl alcohol, acylglycosylsterols and glycoproteins [220]. It is hepatoprotective, tonic, stimulant, emetic, laxative, stomachic and cancer [221]. It is used to treat gout and rheumatism. Ray et al. [222] reported that Momordica charantia extract inhibits breast cancer by modulating cell cycle regulatory genes. This study was conducted in vitro models. An extract of this plant was investigated in human breast cancer cells, MCF-7 and MDA-MB-231, and primary human mammary epithelial cells. This extract was able to decrease cell proliferation and apoptotic cell death was induced. Survivin and claspin expression was inhibited by this extract.

Carthamus tinctorius (Asteraceae)

The parts used are flowers and seeds. It contains palmitic acid, hexadecanolenin, coumaric acid, daucosterol, apigenin, kaempferol, trans-3-tridecene-5, 7, 9, 11-tetrayne-1, 2-diol, trans-trans-3, 11-tridecadiene -5, 7, 9-triyne -1, 2-diol [223]. It is used in colds, flu, fevers, hysteria, anemia, and diabetes mellitus. It is an antioxidant [224] and alpha glucosidase inhibitor [225]. Loo et al. [226] reported the efficacy of this plant in breast cancer. MDA-MB-231 breast cancer cell and normal human mammary gland cell were treated with a compound that contains Carthamus tinctorius. This compound observed inhibition of cell proliferation. Inhibition of cell proliferation was dose dependent. Its cytotoxic activity was more than commonly used cytotoxic drugs.

Viscum album (Viscaceae)

Parts used are stem and leaves. It possesses sinapylflavanone, glucopyranoside, flavanone, hydroxy flavanone and viscin [227]. It is anticancer, cardiac tonic and antioxidant [228]. It is applied in palpitation, vascular spasms, asthma, dizziness, vertigo and headache. Gunver et al. [229] also documented the anticancer activity of this plant in breast cancer.

Calendula officinalis (Asteraceae)

The materials employed are leaves. It has triterpene, glycoside of calendula, butyl ester, flavonol glycosides, and carotenoids [230]. It is anti-inflammatory and anti-cancer [231]. It is applied in carcinoma of the vagina, and cervix. Pommier et al. [232] documented the effectiveness of Calendula officinalis in preventing acute dermatitis during breast cancer irradiation.

Citrullus colocynthis (Cucurbitaceae)

The parts used are seeds and fruit. It contains phytosterol, flavones C-glycosides, saponins, aspartic acid, arginine, colocynthin, colocynthitin and cucurbitacin glycosides [233]. It is used in constipation and carcinoma of the breast [234]. It is an emmenagogue, ecbolic, cathartic, hydragogue and antioxidant [235]. This plant has growth inhibitory activity. Cucurbitacin glucosides have been isolated from this plant. These glycosides prevent human breast cancer cells [234].

Indole 3 Carbinol (13C)

A compound called indole-3-carbinol, which is a plant constituent from cruciferous vegetables like Brussels sprouts and cabbage, alters estrogen metabolism. This compound reliably modulates the endogenous estrogen metabolism towards the production of more catechol estrogens and might thus offer a new dietary approach to lowering risk of breast cancer [236]. **Silibinin and Chrysin**

Previous studies show that chrysin and silibinin have synergistic activity and exhibit strong anticancer activities against T47D breast cells [187, 188]. It is promising that the synergistic effect of action depends, at least in part, on hTERT and cyclin D1 down-regulation. Their prospective activities in the formulated synergism between Chrysin and Silibinin should be confirmed through other in vitro or in vivo studies. Research proves that Chrysin and Silibinin together may emerge as an attention-grabbing strategy based on herbal medicine for breast cancer control [237].

Lactobacillus acidophilus

Hyperestrogenism and breast cancer can be reduced by the dietary intake of lactobacillus acidophilus. The beneficial bacterium assists in metabolizing estrogen correctly in the bowel. Lactobacillus acidophilus, which is in various forms such as capsules, can be prescribed by clinicians for patients with breast cancer [238].

Selenium

Women with breast cancer have been shown to possess selenium levels that are lower than those of women without cancer. Selenium is a trace mineral that is often lacking in refined food diets. A contrary association exists among the prevalence of human breast cancer and concentration of dietary selenium. The adding of Selenium to the food has been revealed to reduce the occurrence of breast cancer [239].

Targeted therapies These are drugs prescribed to manage some types of breast cancer. The mainly familiar targeted treatment is the drug Herceptin [240]. It is prescribed to manage HER2 positive breast cancer. It functions by preventing the cancer cells from developing and progressing [241].

Gene therapy for carcinoma of the breast

Gene therapy is a remedial approach which is regarded to correct specific molecular defects related with the progression or causation of breast cancer [242]. Mutated BRCA1 and p53 genes which are identified as cancer susceptibility gene participates in the cancer progression [243]. Since mutational inactivation of gene activity is reserved to cancer cells in these contexts, cancer gene modification techniques may give an opening for selective targeting without major hazards of normal, noncancer cells [244, 245]. Both BRCA1 and p53 emerge to restrain tumor cells that lack mutations in these genes, indicating that the so-called gene modification techniques may contain broader efficacy than previously considered. Raising awareness of cancer genetics has recognized these and new genes as possible targets for gene substitute treatment [246]. Early patient study of BRCA1 and p53 gene therapy have given a number of indications of possible effectiveness, but have also recognized areas of clinical trials that are wanted prior to these therapeutic strategies may be broadly employed in patients with breast cancer [247].

Oncogenes inactivation

Several oncogenic proteins have been identified and associated with various cancers [248]. The often pragmatic approach in clinical research is the use of antisense alternatives. Oncogenes transcription also may be blocked through the use of adenoviral gene E1A, which inhibit erbB-2 transcription, an alternative useful in treating cancer over expressing this oncogenic protein [249].

Enhancement of cancer suppressor genes

The tumor suppressor gene mutations are associated with the occurrence of several cancers. Certain clinical trials are underway to introduce p53 through adenoviral vectors into various cancers. Similarly, viral vectors have been utilized to introduce a breast cancer gene BRCA1 and retinoblastoma gene into ovarian cancer and bladder, respectively. This strategy will not work under various circumstances, as the mutated gene suggests that the normal gene has dominant negative activity. In the case of the p53 gene therapy, it might be better to rely on a genetic repair method rather than an augmentation strategy [250].

Cancer stem cell therapy for breast cancer

Current investigation in biology of breast has provided the foundation for the cancer stem-cell hypothesis [251]. Two significant aspects of this theory are that cancer arises in progenitor cells or mammary stem cells as an outcome of dysregulation of the normally strongly regulated method of self-renewal. As a result, cancers have and acquire a cellular subcomponent that preserves central stem-cell functions such as self-renewal, which directs differentiation and tumorigenesis that is responsible for cellular heterogeneity. Advances in the field of stem cells have led to the identification of stem cells in normal and malignant tissue of the breast. The investigations of these stem cells have helped to elucidate the source of the molecular complexity of breast cancer in human. The cancer stem-cell theory has a significant role in the timely recognition, prevention, and management of human breast cancer. Dysregulation of stem cell renewal pathways is involved in the development of both sporadic and hereditary breast cancers. These abnormal stem cells may give targets for the improvement of cancer prevention options. In addition, since breast cancer stem cells may be extremely challenging to chemotherapy and radiation, the progress of additional efficient treatments for breast cancer may need the efficient targeting of this cell population [252].

Anti-oestrogens and the prevention of breast cancer

With the success of anti-oestrogens in breast tumor treatment, many research considered their application as a mediator to prevent breast cancer in women at high risk [253, 254]. Tamoxifen is the antiestrogen drug used

most widely in the therapy of breast cancer. Use of tamoxifen as adjuvant therapy after surgery, usually for 5 years, reduces the likelihood of hormone receptor breast cancer recurrence.

Metastatic breast cancer is also managed by tamoxifen. In numerous females, tamoxifen induce the manifestations of menopause such as mood swings, vaginal discharge and hot flushes. Toremifene is one more medicine strongly related to tamoxifen. It is used an alternate drug in postmenopausal female for the treatment of metastatic breast cancer. Fulvestrant is another drug that decreases the estrogen receptor numbers. It is usually useful in postmenopausal female, even in tamoxifen resistant breast cancer. In previous studies, tamoxifen was evaluated for its efficacy in 13, 388 females at higher risk of breast cancer for the period of 5 years. The research showed 49% risk reduction of rising invasive breast cancer and also reduced risk of contralateral breast cancer, recurrence and prolonged survival in the woman who received tamoxifen as adjunct after surgery [187, 188]. Antioestrogens now are recommended as chemoprevention for woman with atypical hyperplasia, familial tendency for cancer and significant family history of breast cancer. They are also prescribed because component of practice post-operative concomitant management of those with estrogen receptor positive cancers for duration of 5 years following surgery [255].

Human monoclonal antibody

Monoclonal antibodies are prepared in the laboratory [256]. These are used alone or in combination with radiation therapy and chemotherapy to locate and target cancer cells. Usually, the body's immune system attack to foreign antigens such as infectious agents. It will then create antibodies to assist fight it off. The body does not identify cancer cells as a kind of foreign attacker. So, antibodies are then not formed. Randomized clinical trial was done to find out the efficacy of denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor κ B (RANK) ligand, when compared to zoledronic acid in preventing skeletal-related events for breast cancer patients with bone metastases. Denosumab proved to be superior than zoledronic acid to prevent or postpone SREs among the breast cancer patients with bone metastasis. It is demonstrated that denosumab is possible therapeutic alternative for individual with bone metastases [257].

Immunotherapy

It uses the body's immune system to fight against the cancer cells [258]. Cancer vaccine is one of its examples. Parts of cancer cells or cancer cells are used for the formation of vaccines. These cells excite the body's immune system to assist assault and destroy cancer cells [259]. Immunotherapy has turn into a significant constituent in the management of breast cancer. HER2 targeted therapy are currently a vital component of HER2 over expressing breast cancer treatment. Trastuzumab, with the new current additions of pertuzumab and TDM1, include significantly better breast cancer prognostication. With numerous Federal Drug and Administration approved antibody therapies utilized in collectively the adjuvant and metastatic environments, advancement continues to be accomplished in the field of immunotherapies. Today's success with targeted therapies, aggressive specific immunotherapy, understanding assure for ongoing success in overall survival within the adjuvant environment. The highly specific and targeted approach of vaccine therapy not only sidesteps the toxicities of recent standard of care therapies, active and passive immunotherapies such as ipilimumab; but offers curative strategy beyond currently the HER2-overexpressing patients. Although vaccines against breast cancers have been largely unsuccessful in prior clinical trials, the majority of these trials carried out in the setting of advanced-stage metastatic disease, unfavorable environments for agents proposed to prevent, rather than treat, disease. With current clinical trials carried out on the adjuvant settings, immunogenicity is in the current signifying association with medical response.

Anti-angiogenesis drugs

Angiogenesis and inflammation are host-dependent manifestations of tumors that can be targeted with impediment strategies long prior to cancer start and develop [260]. Numerous prescription and non-prescription medicines are now accessible for utilization in angioprevention. Angioprevention can be proposed at four levels; first for the healthy people, 2nd for population at enhanced risk of tumor, 3rd for preneoplastic disease and 4th for prevention of cancer relapse. There are numerous achievements in prevention of cancer that reveal medical possibility and levels of interference, from no to slight to strong clinician participation. To evade toxicity whereas maintaining effectiveness, angioprevention desires to attain a level of angiogenesis prevention that is not extremely oppressive, such that hale and hearty vascular activity is maintained. These drugs block angiogenesis. Lack of blood supply to the cancer cells means that they can neither grow nor perish. Several drugs have been explored for the treatment of metastatic breast cancer. They are also explored in the neoadjuvant (preoperative) context in the early stage of breast cancer [261]. Antiangiogenic therapy in breast cancer holds significant promise, and several ongoing studies are attempting to further elucidate the ideal management context and mediator combination. In estrogen receptor positive aliment patients, researches suggest a correlation between endocrine resistance and dependence of cancer on angiogenic networks, suggesting a therapeutic benefit in combining endocrine therapy with antiVEGF mediator. The outcomes of randomized clinical trials highlight the multiplicity in response to antiVEGF therapy and suggest the need for improved selection of patient subsets further to be likely to benefit from these therapies. The identification of biomarkers for therapeutic response is individual component of in-depth scrutiny, although primarily research to this point has proved unable to find a correlation between cancer-related markers such as cancer mutations and EGF expression and scientific response.

Surveillance and follow up

A regular assessment of the important in print literature conducted by de Bock et al. [262], revealed that 40% of recurring cancers are identified in asymptomatic individuals during routine visits. This information intensifies the significance of surveillance and follow-up. Clinical investigation such as history and physical examination is suggested each 4–6 months for 5 years, after that each year with annual mammography. Female on tamoxifen should receive annual gynecologic assessment if uterus is present. Female who experiences ovarian failure due to treatment or on an aromatase inhibitor should undergo monitoring of bone health with a bone mineral density measurement at initiation and sometimes later. Women should be counseled also to embrace other dynamic risk factors, such as reducing alcohol use, lowering BMI and increasing physical activity.

Conclusion

The increase of information on the pathophysiologic mechanisms of breast cancer has brought extensive development in the figure of biomolecular markers. In addition, the development of targeted drug design has grown quickly and more complicated, providing numerous agents that target these markers for in vivo investigation in animal models as well as clinical studies. The enthusiasm among scientists and Physicians about the growing management strategies is tempered by apprehension that resources are insufficient to carry the mainstream of these agents to advanced clinical trials. The challenges, then, are to choose the most capable agents to be investigated and the proper clinical studies for such evaluations. We have adopted a justifying strategy to unfolding the most extensively documented molecular targets in breast cancer. Drugs that amend the NRF have not been evaluated comprehensively so far, and such studies can boost the chances for true ‘endocrine’ strategies for management of breast cancer. Furthermore, agents that amend angiogenesis and apoptosis demonstrate an thrilling area of research, mostly in vigilantly chosen combination regimens.

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