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(REVIEW ARTICLE)

Breast cancer: Risk factors and prevention strategies

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Abstract

Among the cancer diseases, breast cancer is becoming fast growing leading cause of oncologic mortality among women. It is hoped that, evaluation of different dimensions of breast cancer and its associated factors such as environmental and genetic factors, will increase the efforts of prevention. Current studies suggest that mutations in some genes play an crucial role in susceptibility of breast cancer. Thus, researchers aimed to isolate such breast cancer susceptible genes. Some epidemiologic studied also suggested that, moderate to vigorous exercise for 3-4 hours per week can lower the risk for breast cancer for 30%-40% in women than those of the sedentary women. Obese or overweight women have 50%-250% greater risk for breast cancer after menopause. Alcohol use also increases the risk of both postmenopausal and premenopausal breast cancer. Thus, these trends of sedentary lifestyle, decreasing physical activity and increasing obesity may lead to an increase in the incidence of breast cancer. Thus, adoption of healthy food habits, increasing physical activity and changes in sedentary lifestyle may have a great impact on the prevalence of this disease in future. The treatment strategies for breast cancer are broad-ranging depending on tumor's biology; stages of the disease; tolerance, and acceptance of the patient. There is various treatment approaches of breast cancer such as radiology, surgery, and systematic therapy (chemotherapy, endocrine therapy and biological therapy) etc. In this article required information about risk factors and current breast cancer prevention strategies are collected through literature review.

Keywords: Breast cancer; Risk factors; Prevention; Chemotherapy; Radiotherapy

1. Introduction

Breast cancer is one of the most prevalent diseases among women worldwide. The growing malignancy of breast cancer not only impact on health of patients but also mental and social aspects of human life [1]. Approximately, in more than 1.5 million women, breast cancer is diagnosed every year all over the world [2, 3]. Various factors contribute to the incident of breast cancer and thus it is considered as a multifactorial disease [4]. The rate of occurrence of the disease is different in different place worldwide and these differences in the rate are due to different factor like reproductive patterns, hormonal factors as well as early diagnosis of the disease [5, 6]. In the U.S., due to early detection of the disease and improved treatment therapy, the mortality rate of breast cancer has been continuously decreasing [7, 8]. Other risk factors link to variation in the rate of incidence of breast cancer by geographic areas due to genetic difference, exposure to carcinogenic chemicals and individual lifestyle and health behaviors [9]. In a study, by the International Agency for Research on Cancer approximate that, obesity, overweight and a sedentary lifestyle were the cause of about 25% of the breast cancer cases worldwide [10].

Many risk factors of breast cancer can be modified for prevention of breast cancer such as, change in diet; exercise; pregnancy and nursing; avoidance of various things such as exogenous female hormones, alcohol, tobacco in excess, ionizing radiation etc. each of the factors such as inherited, environmental or histopathological factors are important.

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The prevention strategies can be directly addressed to the environmental risk factors to lower the environmental risk. While histopathologic and inherited risk factor cannot be changed directly, but can be indirectly addressed through various tools such as- estrogen and their receptors by chemotherapy or surgical excision of the organ(s) at risk or infect. The risk of breast cancer is also affected by Mammographic breast density which is appears to be influenced by age, body mass index and genetics [11, 12]. Due to the advanced medical therapies and widespread facilities for early screening the mortality rate decreases in America, although the breast cancer incidence rate increases year after year, the development of biological therapies proved to be helpful in curing breast cancer. In this review, the studies will mainly focus on breast cancer related risk factors and prevention strategies of the disease over the past years.

2. Risk Factors of Breast Cancer

Various studies have shown that the risk of breast cancer is due to some factors. The one of the main factors that influences the risk include getting older and being a woman. Besides these two factors, there are numerous others factor of breast cancer.

2.1. Demographic factors

2.1.1. Female Sex

Due to high hormonal stimulation, female sex is one of the main risk factors of increased chance of breast cancer. Some breast cells of women are very vulnerable to hormones like, Estrogen and progesterone and any kind of imbalance in the hormone quantity. Circulating estrogen and androgen have been also shown to be associated with high risk of breast cancer in older age [13, 14]. In case of postmenopausal and premenopausal women, alternation in level of endogenous sex hormones can result in higher probability of breast cancer [13].

In case of men, the malignancy of breast cancer is accounting for less than 1% of all breast cancer. Breast cancer in men most often occurs in older age, on average about 67. Other important factors causing increase chance of breast cancer in men are: hormonal imbalance, exposure to radiation, family history of breast cancer, mutation of BRCA2/ BRCA1 genes and Klinefelter syndrome etc [15].

2.1.2. Aging

Age is also an important known factor for breast cancer after gender [16]. The rate of incidence of breast cancer gradually increases with age and at its peak especially during menopause and postmenopausal period. Approximately 80% of the total breast cancer patients are more than 50 year old age and about 40% are of more than 67 years old [17, 18]. There is relationship between age of the patient and a particular subtype of molecular types of breast cancer, Luminal A subtype generally diagnosed in patients more than 70years, while patients in groups under age of 40, it is Triple-negative subtype [18]. However, breast cancer in women of younger age occurs in advanced stages, larger size, weaker survival and positive lymph nodes [19]. Not only breast cancer, but risk of a vast number of potential carcinogens that results in carcinogenesis and various cellular alternations may also takes palace with age.

2.1.3. Blood Group

The survival and risk for various malignancies have been associated with ABO blood type [20, 21]. A recent showed a possible increased risk of ductal carcinoma in women with blood group A and Rhesus positive [22] and another two studies suggested a possible association of risk of developing familial breast cancer in blood group A or B carriers [23]. However, in case of women having AB blood group with negative Rhesus factor, the risk of breast cancer is generally low [24]. But according to many researchers, there is no relationship of breast cancer with blood group [25].

2.2. Reproductive Factors

The relationship of breast cancer with reproductive factors is mainly related to reproductive hormone which begins to secrete at the age of puberty and continues during menstrual cycle. The important reproductive factors associated with risk of breast cancer are, early menarche, late age at first pregnancy, late menopause and low parity etc. Multiple births, early first birth and long cumulative lactation period act as protective effect not only against risk of developing breast cancer but also against radiation which are associated with risk of breast cancer [26].

2.2.1. Menarche

A study reported that the risk of growing breast cancer increases two times when menarche occurs at younger age [16]. In a cohort study of a large women population of 11,889 in China also reported that menarche occurring younger age is

associated with risk of developing breast cancer [27]. But, in some other studies, there was no risk of developing breast cancer associated with younger age during menarche [28, 29]. An experiment in Italy revealed that there is no relation between duration of menstrual cycles and breast cancer [30].

2.2.2. Menopause

The menopause i.e., age over 50 years has relation with risk of breast cancer [31, 32]. A study reported the correlation of breast cancer with older age in menopause [16]. However, early menopause whether surgical or natural, lowers the risk of breast cancer [33]

2.2.3. Pregnancy

The risk of breast cancer reduced in case of the first full-term pregnancy at early twenties and subsequently increasing number of births [34]. In a study, first pregnancy during older age was an important associated risk factor for breast cancer which was approximately more than six times [16]. In a study found that the risk of ER^+ and PR^+ cancers gets reduced by up to 10% after every full-term pregnancy [35]. The result of another study showed the chance of occurrence breast cancers is more in nulliparous women than women having more than three children [36]. However, based on some study, women having more than five children are in high risk of breast cancer [37]. The chance of developing breast cancer is lower in women, who had preeclampsia during pregnancy or children born to a pregnancy of preeclampsia [38]. The risk of both ER/PR- negative and positive breast cancer lowers in women with history of longer breastfeeding period [39].

2.2.4. Abortion

The findings from an analysis of 53 epidemiologic studies showed that natural or induced abortion does associated with risk of breast cancer [40]. Thus, so far there is no stated evidence of positive relation between abortion and increased risk of breast cancer [41].

2.3. Hormonal Factors

Studies have shown that endogenous estrogen and progesterone level is related to the risk of breast cancer in women. During preeclampsia imbalance level of hormones such a, reduced estrogen and increased level of progesterone along with deviation of other hormones, cortisol, insulin, human chorionic gonadotropin, androgens, corticotrophin-releasing factor, insulin-like growth factor-1 from their physiological range shows protective effect against breast carcinogenesis [39]. Exposure to estrogen is directly associated with the risk for breast cancer. The risk of developing breast cancer increases with increased or prolonged exposure to estrogen, whereas reducing exposure is protective against breast cancer [42]. Thus, factors that increase the number of menstrual cycles are likely to associate with developing breast cancer such as, nulliparity, late onset of menopause and menarche [43] and factors that decreasing the number of ovulatory cycles can be protective which can be attained by longer period of lactation [39] and moderate physical exercises [44].

For the risk of breast cancer, both exogenous and endogenous estrogens are associated. Generally ovary of postmenopausal women produces endogenous estrogen and the risk can be reduced by ovariectomy [45]. The hormone replacement therapy (HRT) and oral contraceptives are the main sources of exogenous estrogen. An experiment by Williams et al. [46] showed that the current use of oral contraceptives have relation in developing breast lobular tumors. However, the risk of developing cancer diminishes in women who stop using contraceptives for more than 5-10 years [47]. Hormone replacement therapy is a process by which exogenous estrogen or other hormones are administered in menopausal or postmenopausal women. A number of studies show the association of HRT with increase risk of breast cancer [48]. However, the risk of developing breast cancer has been shown to decrease significantly, after stopping HRT for two year [49].

2.4. Genetic Factors

Several genetic mutations were reported to be associated with the incidence of breast cancer, but Approximately 40% of carcinogenesis of breast occurs due to mutation of two major genes characterized by high penetrance are BRCA1 (located on the 17^{th} number chromosome) and BRCA2 (located on 13^{th} number chromosome). The mutation of BRCA1 and BRCA2 genes are inherited mainly through autosomal dominant manner, sometimes sporadic mutations are also reported [50]. The findings of a study show that by the age of 70 years, 55%-65% BRCA1 mutation carriers and 45% BRCA2 carriers develop breast cancer [51]. Other highly penetrant genes causing breast cancer are CDH1, TP53, STK11 and PTEN [52, 53, 54, 55]. Studies reported that, DNA repair genes such as, PALB2, ATM, CHEK2 or BRIP1 can interact with BRCA genes and involve in the induction of carcinogenesis of breast; though their degree of penetrance lower than

BRCA1 and BRCA2 genes [56, 57, 58, 59]. A recent study reported that, the mutation of gene XRCC2 could also involve in with a risk of breast carcinogenesis [60]. Addition to other risk factor, changes in human interferon α-2b may also involve in starting or progression of carcinogenesis in breast [61].

2.5. Family History

In various studied family history of breast cancer is mentioned as one of the major factors associated with breast carcinogenesis development [16, 37, 62, 63]. Researchers found that, the risk of developing breast cancer is more likely 11 times more in women with a family history of two or more cases of breast cancer who are negative in terms of BRCA gene mutation [64]. Carriers of BRCA1 and BRCA2 with family history of immediate relatives with early-onset of breast cancer have a risk factor of developing breast cancer [65]. The rate of occurrence of breast cancer is higher in the patients with a family history of breast cancer irrespective of age. This association is potentially triggered by epigenetic changes as well as environmental factors [66]. Women with family history of ovarian cancer with BRCA genes mutation may also induce a risk of breast carcinogenesis [67]. However, a study in a hospital among 5,359 women, found no association between the family history of breast cancer and; the mortality and severity of the patients with breast cancer [68].

2.6. Breast-related Factors

2.6.1. Breast density

The total amount of dense tissue in breast is called as breast tissue, and numerous studies described that breast density is an independent factor which is associated with the risk of breast cancer [69]. The breast density does not remain same throughout the lifetime; and categorized into several types for clinical studies such as, high-density, low-density and fatty breast etc. Greater breast density is observed during the younger age of females and the density decreases with the older age, during pregnancy or breastfeeding period as well as during the period of hormone replacement therapy [70]. Based on study, greater density was associated with increased risk of breast cancer both in postmenopausal and premenopausal women [71]. Result of another study showed that the risk breast cancer especially ER-positive and ER-negative invasive type have relation with breast density, but its rate decreases with the age [72]. However results of some study showed no relation of breast density with breast cancer [63].

2.6.2. Breastfeeding

Breastfeeding or lactation provides protection against breast cancer, and many researchers described the role of breast breastfeeding in protection from breast carcinogenesis [73]. With increasing duration of lactation, the protective effect of lactation against cancer increases [31]. Another case-control study result showed, the risk of developing breast cancer could reduce by up to 50% from the combination of two factors such as two or more child birth and longer lactation period for more than 13 months [74]. Breastfeeding may also increased rate of survival, decreased the rate of recurrence, progress in prognosis; but the effect may vary in different conditions or states [75].

2.6.3. Benign Breast Diseases

One of the prime factors for breast cancer is the histories of benign breast disorders [30, 76]. Generally, the risk of ER-positive and ER-negative invasive breast cancer are linked with benign breast disorders and at different time of age, the risk is different [72]. Another study showed that breast hyperplasia and hormone replacement therapy in patients with benign breast disease are associated with higher risk of growing breast malignancies [77]. However, in postmenopausal women with benign breast disease, the risk of developing breast cancer decreases [78]. The history of non-cancerous breast alterations including, carcinoma in situ, hyperplasia, and other proliferative or non-proliferative lesions in breast also extent the risk remarkably [79, 80]. Researchers from a study concluded that, the connection between the breast cancer and benign breast disease depends on the family history of breast cancer and the histological classification of benign disorders of breast [79].

2.7. Lifestyle Factors

2.7.1. Physical Activity

The result of a study done among 74,171 women of age from 50 to 79 years found that physical activity acts as protective factor against breast cancer and associated in reduction of risk in postmenopausal women of growing breast malignancies i.e., more physical work was correlated with more profits against breast cancer [81]. However, study of Thune et al. pointed that, physical activity showed more pronounced effects against breast cancer in premenopausal women [82]. There are various hypothesis that explain the role of physical activity as protective factor against breast

cancer incidence; it might prevent cancer by altering immune system response, by reducing exposure to endogenous sex hormones or altering insulin-like growth factor-1 levels [44, 83,84].

2.7.2. Body Mass Index (Obesity and overweight)

According to epidemiological studies, obesity is correlated with an increase probability of breast carcinogenesis. Due to this correlation, mainly obese postmenopausal women tend to develop ER-positive breast cancer. And these obese females show poorer clinical outcomes [85]. The association of obesity with breast cancer is due to higher rate of aromatization in adipose tissue in which androgenic precursors converted to estrogen [86]. According to a study, obesity during pregnancy independently associated with risk of long-term malignancies, like breast and ovarian cancer [87]. Body mass index (BMI) plays a role as predictor in survival of patients with breast cancer [88]. According to Wang et al. women above age of 50 years with higher BMI are in greater risk as compared to those with lower BMI [89]. Researchers observed that more aggressive clinical or biological features are associated with patients of greater BMI such as higher percentage of metastasis of lymph nodes and larger size. Especially in premenopausal women, higher probability of cancer relapse and greater percentage of mortality rates might be occur due to obesity [90].

2.7.3. Vitamins

The anticancer properties of vitamins might potentially benefit as protective factor against several carcinogenesis including breast cancer, though the mechanism is not yet understood fully. Currently, most of studies are focused on vitamin D with regard to breast cancer, as vitamin D confirming its potential effects against breast carcinogenesis [91, 92]. The results of some studies found that there is a reverse relation between the serum 25-hydroxy vitamin D and tumor size of the breast cancer patients and high level of serum 25-hydroxy vitamin D was found to be associated with lower risk of breast cancer incidence in both postmenopausal and premenopausal females [91, 93]. From a case-control study, it was found that, as compared to women with normal serum 25-OH vitamin D level, the risk of developing breast cancer 27% increased in women with vitamin D deficiency [94]. Increased expression of vitamin D receptors was found to be connected in lowering the mortality rate because of breast cancer [95].

2.7.4. Diet

Research found relationship between non-vegetarian food and breast cancer [16]. Diet containing low content of saturated and polyunsaturated fatty acids is important against breast cancer [96]. A study showed increased consumption of meat and nonprocessed meat is connected with risk of breast cancer [97]. The result of a study found that in malignant tissues, the concentration of Fe, Zn and Cu higher than benign tissues and that may be the outcome or cause of breast cancer [98]. Highly processed meat is considered as carcinogen by World Health Organization (WHO) which might cause risk of breast carcinogenesis along with gastrointestinal malignancies. With regards to excessive consumption saturated fat, similar observations were made [99]. It was found that, the risk of breast cancer 11% increases with the 10% increase of ultra-processed food [100]. Conversely, a diet rich in lean protein, fruits, vegetables, whole grains and legumes is connected with a lowered risk of breast cancer [101]. Usually, diet which includes food containing high amount of vitamin D, folate, fibre, n-3 PUFA and polyestrogen might acts as protective against breast cancer [102].

2.7.5. Intake of Alcohol

Various studies confirm that excessive intake of alcohol is carcinogenic and it might increase the risk of gastrointestinal malignancies and also link to the risk of breast cancer [103]. European Prospective Investigation into Cancer and Nutrition (ERIC) found a relation between consumption of alcohol and hormone receptor-negative and hormone receptor-positive tumors of breast. And the study showed that the consumption time of alcohol can influence the chance of breast cancer and the risk is increases in females who consume alcohol in period before first full-term pregnancy [104]. Alcohol consumption induced increased estrogen levels and thus hormonal alternation affecting the risk of malignancies within female organs [105].

2.7.6. Smoking

Both active and passive smoking in postmenopausal females and during prenatal periods are related to increased risk of breast cancer [106, 107]. The carcinogens found in tobacco transported into the breast tissue in increases the possibility of causing mutation of the suppressor genes (p53) and oncogenes. Therefore, both active and passive smoking contributes to the induction of carcinogenesis events [107]. Females with a family history of breast cancer, longer smoking as well as smoking before first pregnancy, are additional risk of breast cancer [108, 109].

2.8. Other Risk Factors

2.8.1. Radiation

Mammary gland is very sensitive to radiation related malignancies, especially when exposure takes place at younger age. The knowledge about radiation-associated risk of breast cancer is mainly derived from the study of patients that were exposed to therapeutic or diagnostic medical radiation and from the survivors of Japan's atomic bomb. According to a result of large population-based study, the women that faced with radiation due to diagnostic and therapeutic purposes like, screening of tuberculosis, monitoring of pneumonia or previous cancer treatment have two or three times more risk of developing breast cancer [110]. People that are being treated with whole-lung irradiation and exposure to radiation due to treatment of cancer in childhood are the highest risk of breast cancer; and also rate of mortality due to breast cancer among these individuals is higher [111]. Besides chest radiations, due to high-dose alkylator and anthracycline chemotherapy, the survivors from sarcoma or leukemia are at great risk of breast cancer at younger age [112].

2.8.2. Exposure to Chemicals

Exposure to chronic chemicals can encourage breast carcinogenesis by affecting microenvironment of the breast such as by alternating genes and inducing pro-carcinogenic events in tumors [113]. Various chemicals are suspected to induce breast cancer but, polychlorinated biphenyl (PCB) and dichlorodiphenyltrichloroethane (DDT) are the mostly investigated chronic chemicals in terms of risk to breast carcinogenesis as early exposure to these chemicals prevents the growth of mammary gland [114, 115]. A plausible relation between breast cancer and increased exposure to chemicals such as synthetic fibers, polycyclic aromatic hydrocarbons (PAH), oil mist, insecticides and organic solvents are also observed [116].

3. Prevention Strategies

Based on the biology of the tumors, stages of the disease and tolerance of the patient, the strategies for the treatment of breast cancer are wide-ranging. In clinical and theoretical study of breast cancer and technologies of their prevention great advances have been made. The treatment strategies may include screening, surgery, radiotherapy, biological prevention, and systemic therapies like, chemotherapy and endocrine therapy etc.

3.1. Screening

One of the successful prevention measures of breast cancer is early diagnosis. If the disease is diagnosed at an early stage of metastasis and as a tumors of primary stage, then chemotherapy could effectively work and the tumors could be remove successfully by surgery. Mammography is a screening method used for diagnosis and systematic screening of breast which provides some key qualities such as: minimal technical set-up, easy to perform, easy to standardize, possible to compare with previous mammographies and possible to review [117]. In America, every two years, over 70% women of aged between 50 to 70 years have been undergone mammography for breast cancer screening [118]. Besides America, many other countries with highly developed medical system have also introduced mammography for systematic screening of breast cancer, between age of 50 to 70 years in every 2 years and this effort helps to reduce the mortality due to breast cancer in women of that age group [117]. But the reduced mortality rate was not significant in women aged between 40 to 49 years [119]. The results show the importance of screening programs of mammography for breast cancer.

Another tool that is widely used for the breast cancer is Magnetic Resonance Imaging (MRI). It is most demanding breast cancer examination modality and expensive as well [120]. It is especially used for detecting invasive ductal carcinoma and is more sensitive tool in women with high-risk than mammography [121]. In detection of hidden primary breast cancer, residual tumors after neoadjuvant chemotherapy, auxillary nodal metastasis or other small tumors, MRI is effective [122]. The rate of detection of MRI is ranging from 37% to 100% and specificity of detection is lower than mammography [123].

Breast ultrasound is a great tool in the detection of breast diseases. Most of the breast tumors are visualized on ultrasounds, which are not seen on MRI or mammography. The quality of the breast ultrasound depends on some variables, such as: density of breast glandular tissue, breast size, previous records of radiation or surgeries etc, and that is why it has not been used widely as breast cancer screening tool [124].

3.2. Surgery

Over the past 20 years, tremendous changes have occurred in breast cancer surgery. The surgical procedures that enabling the cancerous tissue are of two major types: Mastectomy and Breast-conserving surgery (BCS). The concept of breast conserving surgery was developed by two physicians, Bernhard Fisher, USA and Umberto Veronesi, Italy in the early 1970s, which involves the removal of malignant tumor combined with local radiation [125, 126]. BCS also called as lumpectomy, partial/segmental mastectomy, quadrantectomy or wide local excision, allows the removal of the cancerous tissues of breast combined with techniques of plastic surgery called oncoplasty. However, mastectomy involves complete removal of breast and associated with reconstruction of breast immediately after removal of breast in most of the cases. BCS seems to be more beneficial, but patients treated with BCS often show a further need of complete mastectomy [127]. The complete removal of breast affected the lymph nodes involves axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB). The use of BCS technique seems to reduced the number of postoperative complications, lowered the psychological burden of the patients, and most importantly the outcomes is cosmetically better [128].

3.3. Chemotherapy

AccordingtoSporn, chemotherapy is process in which natural or pharmacological agents are used that inhibit the growth of invasive types of breast cancer either by reversing or arresting the progression of premalignant cells, or by blocking the DNA damage that initiates the process of carcinogenesis [129]. Chemotherapy is considered as systemic treatment of breast cancer and of two categories: adjuvant and neoadjuvant. Based on the characteristics of the breast tumors, appropriate type of chemotherapy treatment is individualized for the treatment. Neradjuvant chemotherapy can be provides orally or intravenously and usually used for inflammatory breast cancers, locally advanced breast cancer, for downstaging of large size tumors to allow breast- conserving surgery (BCS) or small tumors of molecular subtypes like HER2 or TNBC. Different breast cancer molecular subtypes respond differently to chemotherapy of preoperative periods, thus it is important to choose the proper drug for chemotherapy [130]. Adjuvant chemotherapy with antihormonal medication has proven successful in over 60% patients with positive estrogen and progesterone receptors [131]. Currently, the treatment of chemotherapy involves application of schemes of 2-3 drugs simlutaously, the drugs includes: carboplatin, taxanes (docetaxel, paclitaxel), cyclophosphamide, anthracyclines (doxorubicin, epirubicin), and 5-fluorouracil/ capecitabine etc.

As more than 70% of breast cancers are estrogen receptor (ER) - positive, thus chemotherapy treatment mainly target estrogen receptors. Two major classes of anti-estrogen drugs are: the Aromatase Inhibitors (AIs) and Selective Estrogen Receptor Modulators (SERMs). Tamoxifen (TAM) is one of the famous SERMs compounds that have been used for more than 30 years to treat breast cancer [132]. For the treatment of all stages of breast cancer, tamoxifen (TQM) is used [133]. Many large scale trials have shown that TAM could reduce the risk of both invasive and non-invasive breast cancer and have also shown reduction in ER-positive breast cancer by more than 30% after treatment with TAM for 5 years. But there has been no significant reduction observed in case of tumors of ER-negative breast cancer [134, 135]. However, the TAM therapy also shows some side-effects. In TAM- treated patients, especially among women older than 50 years, the risk of deep-vein thrombosis, pulmonary embolism, stroke and endometrial cancer is increased [136].

Raloxifene, a second generation drug of SERMs has been approved for the treatment of breast cancer of invasive type in women of osteoporosis as well as post menopause and heart disease and has fewer side-effects than TAM [137]. In a trial of the Study of Tamoxifen and Raloxifene (STAR) demonstrated that the effectiveness of raloxifene is less than TAM [135]. Raloxifene shows no significant effect in case of lobular and ductal carcinoma. However, due to its less side-effects, raloxifene is still considered as good therapeutic option for invasive breast cancer type. Several third generation SERMs drugs have also been discovered such as, arzoxifene, ospemifene, bazedoxifene (BZA) and lasofoxifene (LFX), but only BZA has reached clinical used stage [138].

Currently, in patients of postmenopausal breast cancer Aromatase Inhibitors (AIs) drugs are b used as the first line treatment therapy instead of TAM. Biosynthesis of estrogen from androgen is catalyzed by an enzyme called aromatase and AIs inhibits aromatase to reduce the level of estrogen in plasma [139]. Steroidal inhibitors and non-steroidal inhibitors are two classes of AIs. However, third generation AIs: exemestane (steroidal inhibitors) and anastrozole, letrozole (non-steroidal inhibitors) shows approximately same efficacy in breast cancer prevention. The study of many trials have showed that AIs are more potent than TAM in reducing the rate of incidence of breast cancer both as monotherapy and after 2-3 years of tamoxifen treatment [140, 141, 142, 143]. Various side-effects are associated with treatment with AIs; the increase risk of osteoporosis is the major side effect. Other side-effects including, incidence of tunnel syndrome; joint pain, and stiffness; or dysregulated metabolism of lipid; however these side-effects have lower impacts of the quality of a patient's life. The cancer cells acquired resistance against AIs as well as SERMs after prolonged

treatment, have been observed. The cancer cells acquired resistance to AIs due to crosslinks between estrogen receptor pathways and various other signaling pathways such as Akt/PI3K/mTOR and Raf/Ras/MAPK/MEK [144].

Currently, though chemotherapy is considered as effective preventive measure, but it often causes several side-effects such as, vomiting/nausea, hair loss, mouth sores, diarrhea, increased susceptibility to infection, fatigue, anemia, bone marrow suppression, leucopenia, cardiomyopathy, neuropathy and impaired mental functions etc. electrochemotherapy, a special type of chemotherapy used in case of breast cancer that has spread to the skin, it is still not available in most clinics.

3.4. Radiation Therapy

Breast radiation therapy is a local treatment which is an integral part of breast cancer, basically provided after chemotherapy and/ or surgery. The radiation therapy is performed to confirm that the cancer cells remain destroyed and also to minimize the chances of recurrence of breast cancer. Radiation therapy is suitable in case of unresectable and metastatic breast cancer [145]. Depending on specific clinical features and previous type of breast cancer surgery, the proper type of radiation therapy selected. Most common techniques used are, chest-wall radiotherapy (generally used after mastectomy), breast radiotherapy (usually applied after breast cancer), and breast boost (applied after breast cancer surgery) etc. breast cancer radiotherapies are distinguished into several types, (1) 3D- conformal radiotherapy (3D-CRT), (2) intraoperative radiation therapy (IORT), (3) brachytherapy and (4) intensity-modulated radiotherapy (IMRT). Besides importance, these radiation therapies also show some side-effects. Common side-effects of radiation therapy applied in patients with breast cancer are fatigue, lymphoedema, and darkening and irritation of the radiation exposed skin. However, radiation therapy significantly lowered chance of breast cancer recurrence and improved overall patient's survival rates [146].

3.5. Biological Prevention Therapy

Currently, the monoclonal antibodies are used for the treatment of breast cancer, known as biological prevention has been developed to improve the quality of patients with breast cancer. Biological therapy can be provided to patients at any stages of the therapy of the breast like: as neoadjuvant therapy before surgery or as adjuvant therapy after surgery. One of the main target of the biological therapy i.e., monoclonal antibodies is HER2. So, in case of HER-2 positive breast cancer patients, biological therapy is common; and major drugs include pertuzumab, trastuzumab, trastuzumabderuxtecan, neratinib and lepatinib [147, 148, 149, 150, 151]. A humanized recombinant monoclonal antibody Trastuzumab (Herceptin) is fist drug targeted HER2 approved by Food and Drug Administration (FDA). This drug can directly interact with HER2 [152, 153]. Trastuzumab activate the immune system against cancer cells by in habiting the PI3K/Aktand MAPK pathways or by a mechanism called antibody-dependent cell-mediated cytotoxicity (ADCC) [154, 155, 156]. In trastuzumab treated patients, side-effects such as left ventricular ejection fraction (LVEF) declined and congestive heart failure were found [157].

Another humanized monoclonal antibody Pertuzumab (Perjeta), like trastuzumab can bind with the extracellular part of HER2. But the binding domain is not similar [158]. For the treatment of HER2-positive breast cancer, the combination of pertuzumab with trastuzumab and docetaxel has been approved [159]. Common toxic side-effects of pertuzumab-treated patients are febrile neutropenia and diarrhea. Other recombinant monoclonal anti-VEGF antibody (rhuMAb VEGF) or bevacizumab are investigated for their efficacy of inhibiting angiogenesis [160].

In case of pre-menopausal women with Luminal, and HER2-negative breast cancer, everolimus-TOR inhibitor with exemestane and in postmenopausal women CDK4-6 inhibitor ribociclib or palbociclib received simultaneously, with hormonal therapy [161, 162, 163]. For triple-negative breast cancer atezolizumab is approved while for HER2-negative and estrogen-positive breast cancer, two penultimate drugs along with everolimus and abemaciclib can also be used [164, 165, 166]

4. Conclusion

Breast cancer disease developed in breast tissues including lobules and ducts. Breast cancer is not only involved with patient, but also with patient's family and community, and wastes many financial and spiritual resources. This disease is not gender specific but hardly occurs in men. There are different risk factors for different types of cancer. Although many factors have been identified as cause of breast cancer development, but its exact mechanism is not clear. The process of breast cancer diagnosis and treatment has undergone enormous changes over the last two decades. But, breast cancer is still one of the most common forms of cancer and causes mortality among women, especially mortality rate is higher in less developed country. The researcher need to include development of – some tools that enable to accurately identify women at high risk of breast cancer; preventive chemicals with low side effects; effective education

, and communication of risks and benefits of chemotherapies; and means to combine various risk-reduction approaches. Moreover, during the illness, family and social support can reduce most of its negative impacts as this disease affects not only physical but also mental and social position of the women's life.

Compliance with ethical standards

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