Recent Studies & Advances in Breast Cancer

Chapter 2

Chemoprevention in Breast Cancer

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1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide. It represents the significant health problem imposing an enormous socioeconomic burden on healthcare system. Among cancer related deaths, breast cancer is the second leading cause of death. Its global incidence and clinicopathological presentation varies markedly depending on the region and ethnicity, being highest in western developed countries. But because of modernization, dramatically changed lifestyle and altered pattern of reproductive behavior, prevalence of breast cancer is rising in the developing countries also. Nearly 25% of all cancers cases are comprised of breast cancer with an estimated 1.67 million new cases diagnosed in 2012 [1]. More than 500000 deaths are recorded every year due to breast cancer [2]. The reported incidence of breast cancer among women at high risk is 43.4 per 1,000 per years.

2. Risk Factors of Breast Cancer

Breast cancer is a multifactorial disease. Well-documented risk factors for breast cancer include age, genetic predisposition, endocrine factors, dietary habits and environmental factors. These risk factors can be categorized into two classes- reproductive and non-reproductive. Reproductive risk factors are age at menarche, age at full term pregnancy, parity, spacing of birth, lactation, abortions, age at menopause, use of oral contraceptives and hormone replacement therapy (HRT). Among non-reproductive risk factors, age, nutritional status, physical activity, obesity, height, weight changes during adulthood, family history of breast cancer in first-degree relatives, radiation therapy to chest wall and environmental factors [3,4]. Increasing age is the strong risk factor for breast cancer. In family history, number, degree and age of

affected relative are important in risk assessment. Early age at menarche, late menopause, nulliparous states are the strong reproductive risk factors. Prolonged breast-feeding reduces risk of breast cancer. Mammography is an important screening tool that helps to define underlying risk. Women with more than 60-75% dense tissue on mammogram have four fold to six fold risk of developing breast cancer than women with little or no density [5].

3. Risk Assessment: Key Step in Preventive Strategy

Identification of women at high risk to develop breast cancer is the key step in the preventive strategy. Breast cancer risk can be categorized into three groups- average, high and very high. Women without family history of breast cancer or past history of precancerous breast biopsy are considered to have an average risk. They have 12% lifetime risk of developing breast cancer. High risk is defined as the women with positive family history, 5-year Gail model risk > 1.7%, history of atypical hyperplasia, lobular carcinoma in situ, high mammographic breast density, history of radiation therapy and International Breast Cancer Intervention Study model risk >20%. Women with strong hereditary predisposition and BRCA1/2 gene mutations are considered as very high-risk individuals [6]. Women with average or moderate risk can be managed with lifestyle behavioral modifications and regular mammographic screening. But women in high-risk category need further steps of genetic counseling, enhanced screening with MRI in addition to mammography and preventive therapy with pharmacological interventions. In case of very high-risk group, like BRCA mutation carriers, one can have option of prophylactic surgery [7].

Some risk assessment tools have been proposed, developed and validated in different populations for screening purpose at community level. Gail model is a risk predictor tool using assessment of the risk factors- family history, prior biopsies, number of pregnancies, and age at first delivery. Individuals with high risk can be further targeted for genetic studies for mutation in BRCA1 and BRCA2 genes. High-risk women can be offered different preventive modalities like prophylactic surgery, chemoprevention and surveillance. The use of medications over a five year time period to reduce breast cancer incidence (chemoprevention) has been recommended for women at increased risk of breast cancer. A personalized risk-based assessment and management approach involves an individualized understanding of the risks and benefits of each intervention. Timely identification of women at risk of developing breast cancer is the most important step in preventive therapy.

4. Interplay between Estrogen and Breast Cancer

Endocrinal factors play important role in the etiology of breast cancer. Menarche at an early age, late age at first pregnancy, nulliparity and late age of onset of menopause are the well recognized reproductive risk factors. This reproductive behavior causes prolonged exposure to elevated levels of sex hormones. Estrogens are considered to play major role in promoting

proliferation of normal as well as neoplastic breast epithelium. Numerous epidemiological and clinical studies support increased risk of breast cancer among women using oral contraceptives and HRT.

Cumulative and sustained exposure to estrogens has been linked with increased risk of breast cancer. Exact mechanism of role of estrogen for its carcinogenic effects in breast tissue is not fully understood. But, three mechanisms has been postulated to explain role of estrogen in the causation of breast cancer- stimulation of proliferation of epithelial cells through their receptor mediated hormonal activity, direct genotoxic effects through cytochrome P450 mediated metabolic activation to increase mutation rates and by aneuploidy [8-10]. Recently carcinogenic property of estrogen has been explained by induction of complete transformation of human breast epithelial cells MCF-10F in vitro. All these actions of estrogen can explain its role as an initiator of breast cancer among women [11].

5. Chemoprevention of Breast Cancer

Cancer chemoprevention is the chronic administration of a synthetic, natural or biological agents to reverse, suppress or prevent either the initial phase of carcinogenesis or the progression of premalignant cells to invasive diseases. It is preventive intervention which can decrease cancer related morbidity and mortality [12]. With the better understanding of pathophysiology of carcinogenesis, use of chemotherapeutic agents that halts the development of malignancy has arose interest of researchers in past decade. Chemopreventive agents have effects on different stages of carcinogenesis like tumor initiation, promotion and progression. It is a risk reduction option for women with high-risk of breast cancer. Different mechanisms have been postulated for their action of blocking carcinogenesis.

Primary chemoprevention is the administration of chemopreventive agents to general healthy population without overt disease but with strong risk factors. In secondary chemoprevention, individuals with premalignant lesions are identified and targeted with chemopreventive agents to halt their progression to invasive cancer. Tertiary chemoprevention is defined as administration of the chemotherapeutic agents to prevent recurrence or second new primary malignancy in individuals who have completed treatment of early disease successfully [12, 13]. Prerequisite for chemoprevention is the assessment of high-risk individuals in population. Determination of appropriateness of chemoprevention depends on 5 year Gail Model risk score of at least 1.66% [14]. Options of preventive therapy have been expanded in the past two decades to include two classes of drugs chiefly- selective estrogen receptor modulators and aromatase inhibitors.

6. Selective Estrogen-Receptor Modulators (SERMs)

Estrogen is the key hormone that contributes to normal development and growth of

mammary glands. It also promotes the development and progression of breast cancer in women with high levels of circulating plasma estrogen. Tremendous revolution in the field of potential endocrine manipulative agents has changed the management and outcome of breast cancer drastically. Their role in preventive therapy also has been studied extensively with the assessment of risk/benefit ratio among high-risk women. their trials are also ongoing among different populations. Tamoxifen, raloxifene and third generation SERMs have evaluated widely as therapeutic targets in the preventive management of breast cancer. Anti-estrogens like tamoxifen, raloxifene, anastrozole and exemestane have been studied widely for chemoprevention of breast cancer among high-risk women. Their use was found to be associated with 30-70% reduction in the incidence of breast cancer.

I. Tamoxifen

Tamoxifen was the first drug, which generated the concept of SERM based on structure-function relationship. It is one of the most effective drugs in breast cancer treatment. It is an anti-estrogen drug that blocks the attachment of estrogen to breast cancer cells, thereby preventing the activity of estrogen. Tamoxifen was the first drug tested in trials as adjuvant chemotherapy in breast cancer patients. A meta-analysis of 55 trials of adjuvant tamoxifen therapy reported that there was reduction in the risk of developing new cancer in contralateral breast by 47% among women who received tamoxifen for 5 years. This was a landmark finding suggesting the possibility of potential role of tamoxifen in the field of chemoprevention of breast cancer. Numbers of SERMs were studied for chemoprevention of breast cancer. Tamoxifen remained the first drug of choice for chemoprevention in premenopausal women. Its utility in preventing estrogen receptor (ER) positive breast cancer outweighed the risks of adverse events. Prevalence of side effects of tamoxifen like thromboembolic events, endometrial cancer is more among postmenopausal women compared to premenopausal. First largest trial in United States, NSABP-P1 reported beneficial effect of tamoxifen in reducing breast cancer among high-risk women from 43.4 to 22 per 1000 at five years. Women with ductal carcinoma in-situ (DCIS) demonstrated reduction in the ipsilateral and contralateral invasive breast cancers with administration of tamoxifen [15]. A meta-analysis of 10-year individual data from randomized SERM trials documented a 38% reduction in the breast cancer incidence and 51% reduction in ER-positive tumors. The preventive effect of tamoxifen can last for 20 years [16]. International Breast cancer Intervention Study I (IBIS-I), double blind, randomized placebo-controlled trial evaluated the efficacy and safety of tamoxifen among high-risk pre- and postmenopausal women. They observed 27% reduction in risk of breast cancer. But there was increased likelihood of adverse effects like endometrial cancer, thromboembolic events, hot flushes and night sweats. The highest reduction in risk was seen in invasive oestrogen receptor-positive breast cancer (HR 0·66 [95% CI 0·54–0·81], p<0·0001) and ductal carcinoma in-situ (0·65 [0·43–1·00], p=0·05), but no effect was noted for invasive oestrogen

receptor-negative breast cancer (HR 1·05 [95% CI 0·71–1·57], p=0·8). Results of the study showed that tamoxifen offers a very long period of protection after treatment cessation, and substantially improves benefit-to-harm ratio of the drug for breast cancer prevention [17]. J Cuzick et al reviewed and updated the combined data of five randomized prevention trials comparing tamoxifen or raloxifene with placebo. They focused on incidence of breast cancer, endometrial cancer, vascular events, all-cause mortality and morbidity due to all these causes. They observed 38% reduction in incidence of breast cancer (95% CI 28-46; p<0.0001). In tamoxifen prevention trial, prevalence of ER positive cancer was observed to be reduced by 48% (36-58; p<0.001). But, rise in the rates of endometrial cancer was observed in tamoxifen trial with relative risk of 2.4 (1.5-4.0) and in adjuvant trial at R R. 3.4 (1.8-6.4). while in raloxifene group such side effect of endometrial cancer was not observed [18]. Tamoxifen can reduce the risk of ER positive breast cancer. Now researchers need to find appropriate new approaches to prevent ER negative breast cancers with favorable risk/benefit ratio.

II. Raloxifene

Raloxifene is the drug used for the management of prevention of osteoporosis. Its use is indicated among postmenopausal women only. The efficacy of raloxifene as a chemopreventive agent has been studied in randomized clinical trials against placebo and tamoxifen. Continued Outcomes of raloxifene Evaluation (CORE) trial was the secondary trial to compute the incidence of breast cancer among 4011 postmenopausal women with osteoporosis during extended follow up of 96 months. Results of the trial reported RR of ER positive cancer 0.24 (0.22-0.40) [19]. Study of tamoxifen and Taloxifene (STAR) trial, the largest comparative trial evaluated efficacy of tamoxifen versus raloxifene among 19747 postmenopausal women with Gail score of more than 1.66%. This cohort was followed up for the period of 81 months. With raloxifene, RR of ER positive breast cancer was 1.24 (1.05-1.47). Raloxifene was found to be 24% less effective than tamoxifen at preventing invasive breast cancers, but with fewer adverse events. Most significant finding of STAR trial was the lack of proliferative effect of raloxifene on endometrium and comparatively lower incidence of thromboembolic events supporting the use of raloxifene among high-risk postmenopausal women with uterus [20]. Randomized clinical trials of raloxifene among the high-risk postmenopausal women reported similar risk reduction benefits [20, 21]. As per the breast cancer chemoprevention guidelines from the American Society for Clinical Oncology (ASCO), tamoxifen is a drug of choice for high-risk premenopausal women and postmenopausal women with a hysterectomy, whereas raloxifene may be preferred for high-risk postmenopausal women with an intact uterus [14]. A better understanding of risk/benefit profile of anti-estrogens may have impact on the patient's decisions regarding chemoprevention. Freedman et al proposed models to predict the risks and benefits of SERMs for chemoprevention for women over the age of 50 years, based upon age, race/ethnicity, breast cancer risk, and presence of a uterus [22]. Such tools can aid the physi-

cians in providing women with a more personalized risk-benefit profile for higher uptake of SERM use in chemoprevention of breast cancer.

III. Third generation SERMs

New third generation SERMs have been evaluated for their efficacy in breast cancer prevention with favorable risk/benefit ratio. Lasofoxifene, arzoxifene, ospemifene and bazedoxifene are third generation SERMs agents assessed for the treatment of osteoporosis and breast cancer prevention. In Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) trial, 8556 postmenopausal women with osteoporosis randomized to 0.5 mg of lasofoxifene were followed up for 5 years versus placebo. Trial findings reported 79% reduction in breast cancer in the study group [23]. Another GENERATION trial randomized postmenopausal women to arzo fene versus placebo and found 70% reduction in ER positive breast cancer. But this trial was associated with higher incidence of thromboembolic and gynecologic adverse effects [24].

Reimers LL et al assessed the uptake of chemopreventive antiestrogen agents among high-risk and with ductal carcinoma in-situ. They observed statistically significant difference in choosing option of chemoprevention according to education and potentially by race/ethnicity. Among high-risk women evaluated for breast center, antiestrogen use for chemoprevention was relatively high as compared to the previously published data [25].

7. Aromatase Inhibitors

Estrogen is the main culprit in breast carcinogenesis and aromatase is an enzyme that converts androgen to estrogen. Aromatase inhibitors can block synthesis of estrogen effectively. Reduction in synthesis of estrogen decreases risk of breast cancer. Anastrozole is an aromatase inhibitor that prevents the recurrence and development of new contralateral breast cancer in postmenopausal women. Several trials supported superior role of aromatase inhibitor over tamoxifen in the prevention of development of new breast cancer in postmenopausal women. Unlike SERMs, less side effects of gynecologic or thromboembolic episodes are associated with aromatic inhibitors, but these drugs may cause an increased risk of osteoporosis, musculoskeletal pain, arthralgia and hyperlipidemia. There are no reported trials comparing efficacy of aromatic inhibitors to SERMs in the primary prevention [25].

International Breast cancer Intervention Study II (IBIS-II), double blind, randomized placebo-controlled trial evaluated the efficacy and safety of anastrozole as chemopreventive therapy for breast cancer among 3864 high risk postmenopausal women against placebo. Participants received 1 mg oral anastrozole daily for 5 years and the primary endpoint was histologically diagnosed cases of breast cancer. After follow up of 5 years, 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard

ratio 0·47, 95% CI 0·32–0·68, p<0.001). Predicted cumulative incidence after 7 years reported was 5·6% in the placebo group and 2·8% in the anastrozole group. 18 deaths were reported in anastrozole group and 17 in the placebo group, without any specific cause (p=0·836). Findings from the data of this trial suggest anastrozole is the most effective agent to reduce breast cancer in high risk postmenopausal women. Also they commented that most of the side effects due to deprivation of estrogen were not attributed to the treatment [26].

7.1. Letrozole

It is a third generation aromatase inhibitor with high selectivity. It inhibits estrogen synthesis in peripheral tissues, which is a major source of estrogen among postmenopausal women. It is widely used in advanced, recurrent or metastatic breast cancer treatment and is found to be associated with significantly improved outcome and disease-free survival. Women with germ line BRCA1 or BRCA2 mutations are extremely high-risk individuals for developing breast cancer. Prophylactic mastectomy is one of the options to reduce the risk. But, it is not widely accepted by many women because of its impact on quality of life. Among postmenopausal women with hormone receptor positive early breast cancer, 5-year aromatase inhibitor is a standard line of treatment. Canadian Cancer Trials group MA. 17R tested efficacy of extending their treatment with letrozole for additional five years among 1918 women with early stage breast cancer. It was double blind placebo-controlled trial and primary end point was disease free survival. In comparison to the patients receiving hormonal therapy for 5 years, the group of subjects who received additional treatment of 5 years had significantly improved disease-free survival [27]. In early trials of breast cancer therapy, both non steroidal and steroidal aromatase inhibitors reduced incidence of contralateral primary breast cancers more than tamoxifen did after 5 years of tamoxifen therapy. Additional therapy with letrozole resulted in a further reduction of incidence by 46%, as compared with placebo [28].

Letrozole is a drug under investigation by many researchers currently for primary and secondary chemoprevention of breast cancer. In LIBER trial which is double blind, randomized phase III trial, efficacy of letrozole versus placebo is under evaluation among postmenopausal women with BRCA1/2 mutations [29]. LATER study in New Zealand enrolled postmenopausal women with breast cancer treated with hormonal therapy at least one year ago and currently free of breast cancer. Postmenopausal women who had completed more than 4 years of endocrine therapy for hormone receptor-positive early breast cancer at least 1 year prior, letrozole significantly reduced late invasive breast cancer events. There was a trend towards a disease free survival benefit, but no differences were obsereved in overall survival or cause-specific mortality. This trial contributes to emerging evidence that 10 years of any endocrine therapy is efficacious; but due to limited accrual and small number of events, the results cannot be considered conclusive [30]. A multicenter clinical trial is also ongoing to compare the disease-free survival of women with primary breast cancer treated with letrozole v/s placebo after

completing approximately 5 years of aromatase inhibitor therapy. Eligible women will receive either oral letrozole or placebo drug once daily for 5 years after baseline assessment.

7.2. Exemestane

It is oral steroidal aromatase inhibitor that offers a new option for breast cancer prevention in postmenopausal women at high-risk. By blocking the action of aromatase enzyme, which is required for synthesis of estrogen, exemestane lowers the levels of estrogen. It is irreversible steroidal type 1 inactivator and structural analogue of 4-androstenedione. By suicide inhibition, it prevents conversion of androgen to estrogen. Among postmenopausal women, main source of estrogen is via this step only, which takes place in various peripheral tissues including breast. Its use is advocated among postmenopausal ER positive breast cancer women as an adjuvant therapy. Preclinical and clinical studies advocated the use of exemestane in breast cancer prevention trials because of its antiestrogenic and mild androgenic activity [31].

Large randomized placebo controlled mammary prevention (MAP 3) trail was conducted by National cancer institute of Canada clinical trials group to assess the effects of exemestane on incidence of invasive breast cancer. The study enrolled 4560 postmenopausal high-risk women and randomized them to two groups- exemestane and placebo. After medians follow up of 35 months, RR of ER positive cancer was 0.35 (0.18-0.70) without serious adverse effects [32]. Goss PE et al studied role of exemestane as chemopreventive agent among 4560 postmenopausal women whose risk assessment was done with Gail risk score. In this randomized, placebo-controlled, double blind trial, particpants with median of 2.3% were assigned to either exemestane or placebo group. At median follow up of 35 months, 65% relative reduction was observed in the annual incidence of invasive breast cancer and 53% reduction in all types of breast cancer. Favourable risk-benefit ratio with strong preventive effect and excellent safety profile has been reported with exemestane among high-risk women for breast cancer [33].

Patients' acceptance for tamoxifen and raloxifene in chemoprevention of breast cancer is poor because of their serious side effects. Anastrozole and exemestane emerged as the treatment of choice for reduction of risk with favorable risk/benefit ration among high-risk postmenopausal women.

8. NSAID as Chemopreventive Agents

NSAIDs inhibit the cyclooxygenase (COX), a rate limiting enzyme of prostaglandin synthesis. COX has 2 isoenzymes- COX-1 and COX-2. Out of these, COX-2 is an inducible form. Pro inflammatory stimuli induce and upregulate the COX-2 isoform. Overexpression of COX-2 causes mutagenesis, angiogenesis, inhibition of apoptosis and aromatase-catalyzed estrogen biosynthesis. This causes human breast carcinogenesis. Hence, if COX-2 inhibitors

are administered, blockade of prostaglandin biosynthesis can inhibit growth and development of mammary carcinogenesis [34-36].

Women's Health Initiative (WHI) study examined the effects of regular use of NSAIDs on the risk of breast cancer among 80,741 postmenopausal women with an average follow up of 43 months. In this cohort, they identified 1,392 adjudicated breast cancer cases. During baseline assessment, in detail demographic profile, risk factors and history of use of NSAIDs was recorded. Use of any NSAIDs for at least 5 years was found to be associated with 19% risk reduction in the RR of breast cancer. This large prospective study supported the evidence of chemopreventive effects of NSAIDs against risk of breast cancer. Analysis of the results of this study documented overall 21% reduction in the risk of breast cancer who took NSAIDs at least twice a week for last 5 years and 25% decrease among women taking these agents for last 10 years in comparison to those with no or minimal use. Protective effects of NSAIDs were more profound among high-risk women with high BMI, positive family history of breast cancer, physically less active and taking HRT [37].

9. Metformin in Breast Cancer Prevention

Metformin is adenosine monophosphate protein kinase activator used commonly in type 2 diabetes mellitus for glycemic control. Extensive research showed its inhibitory effect on the growth of mammary cancer cells. Retrospective data demonstrates reduced prevalence of some cancers including breast cancer among patients receiving metformin for other purposes. It is easily available, economical drug with minimal side effects. Hence it is a promising therapeutic agent in the field of chemoprevention of breast cancer [38]. Overweight and obesity are well established risk factors for breast cancer among postmenopausal women and are likely to be attributed to the deranged metabolic profile [39]. Association studies and laboratory studies have demonstrated its potential to decrease the risk for development of cancer, including breast cancer. Recent pilot clinical studies in breast cancer patients suggest that metformin may only be effective in overweight or obese women with metabolic disturbances. Hence, researchers are now investigating the efficacy of metformin for prevention of breast cancer among high-risk women with disturbed metabolic profile (ongoing clinical trials NCT01793948 and NCTO2028221).

10. Other Chemopreventive Agents for Breast Cancer

As the load of breast cancer is rising rapidly, new research interest is emerging in evaluating efficcy and associated adverse events with different chemopreventive drugs. Statins which are lipid lowering drugs and inhibitors of HMG-CoA reductase may have preventive role in chemoprevention of breast cancer. But the results of the studies are inconclusive. Bisphosphonates are the aromatase inhibitors used for management of osteoporosis. Their role in risk reduction of breast cancer by 30% has been reported in population based studies.

Bisphosphonates were found to be beneficial among estrogen negative breast cancers as well, but with the side effect of osteonecrosis of jaw [40-42]. Tibolone, a synthetic steroid, fenretinide, a vitamin A derivative, lapatinib, melatonin, curcumin and vitamin D_3 are the different options for choice in chemoprevention of breast cancer. Some of them are under evaluation in terms of prevention in the ongoing clinical trials [43].

Although many pharmacological agents like tamoxifen, raloxifene, and exemestane and anastrozole have been found to be beneficial to reduce breast cancer incidence, emerging evidence suggests that raloxifene or aromatase inhibitors may be better choices in postmenopausal women. Women avoiding combined hormone therapy with estrogen plus progestin will have lower breast cancer risk. New strategies to adopt the uptake of available breast cancer risk reduction interventions need to be developed.

11. Factors Affecting Acceptance of Chemoprevention for Breast Cancer

The success of any preventive therapy to reduce the prevalence of breast cancer depends on the patients' uptake and compliance to therapy. It is estimated that more than 10 million women are eligible for chemoprevention [44]. Despite of the recommendations and high prevalence of women at high-risk to develop breast cancer, acceptance for chemoprevention among these women has been observed to be limited. There are several factors that affect adherence to the adequate level of prophylactic therapy from physicians' as well as patients' side. These limiting factors are comprised of socio demographic, psychological and clinical factors. The discovery and testing of new agents depend on the acceptability to population. One of the important factors is cost-benefit of the prophylactic drug. Despite of the reduction in incidence of breast cancer with the trials of aromatase inhibitors and antiestrogen drugs, uptake for chemoprevention by high-risk women remained a major dismal. Ropka et al reported less than 5% uptake for the use of tamoxifen for primary prevention of breast cancer [45]. In LIBER trial, overall there was only 15% uptake among all eligible women who were BRCA2/2 mutation carrier. Reasons for refusal of chemoprevention were potential side effects, probability to be randomized to placebo group and lack of support from physician. Roetzheim et al examined likelihood of accepting chemoprevention and completing five years of therapy among 219 women whose breast cancer risk was > 1.7%. They also studied potential clinical and demographic predictors of the outcome in this cohort. Out of 219, 54.4% women opted the choice of chemoprevention and started the therapy. Out of them, 49.2% women stopped the therapy. Women with high risk score with specific risk factors like lobular carcinoma in situ, atypical ductal hyperplasia and osteoporosis were more likely to accept the preventive therapy. The cost of any medical intervention has to be placed in context of clinical benefits that the intervention provides [46].

Smith SG and colleagues systematically reviewed 24 studies to find out factors affecting

uptake and adherence to the therapeutic preventive agents in high-risk women. After thorough analysis of different qualitative and quantitative data, they observed low uptake and adherence to chemoprevention therapy among high risk women. In this meta-analysis including over 21000 women, only one in six women decided to opt for the preventive therapy or to enroll in the clinical trial. Uptake was found to be higher in trials, but very few subjects were interested in continuing for long term in clinical settings [47]. Factors from clinicians point of view are-clinician's attitude towards implementation of preventive therapy in routine patient care setting, prescribing concerns with discussion of medications, time for counselling of the patients, information about risk-reduction strategies, strength of recommendation for chemoprevention and unawareness about the use of chemopreventive agents. Thus, side effects and unawareness about chemoprevention among both patients as well as primary care physicians are the major contributing factors for low uptake of the preventive therapy. Hence, first clinicians should be convinced and trained for baseline risk assessment and emphasis on the preventive strategy among high-risk women.

Healthy women are usually reluctant to take chemopreventive agents for prevention of breast cancer. Major concern in this regard is the side effects of drugs. Important factors that decide the uptake of chemoprevention among high-risk women are their willingness to opt for long term preventive intervention, less interest in chemoprevention, insufficient knowledge and misconception about chemoprevention, cost of the drugs and level of education. Women's perception about breast cancer risk is one of the important motivating factor to accept and adhere to the chemoprevention. Chemoprevention offers a promise in preventive strategy to reduce mortality and morbidity from breast cancer among women at risk.

12. Chemoprevention for Breast Cancer in Clinical Settings

While implementing chemoprevention as a prophylactic measure among high-risk women, risk-benefit ratio should be taken into consideration. Accurate identification of eligible high-risk women for chemoprevention remains a challenging job in the field of preventive oncology. There should be development of promising risk assessment tools with great specificity, sensitivity and higher predictability. Gail's statistical risk model was not adopted by the physicians in clinical settings [48]. Recently Chemoprevention Indication Score (CIS) including patients' comorbidities was proposed. It is user friendly, easy to compute risk calculator that help the clinicians and patients to decide eligibility for chemoprevention [49]. Another issue in the practice of chemoprevention is lack of biomarkers that can act as a powerful predictor response to preventive therapy. Currently breast density is the promising predictor of response to chemoprevention and with tremendous advances in the technologies it will become more popular and helpful biomarker. Breast cancer detection relies chiefly on mammography. But it has been found to be associated with risk of false positive results. Mammography also has limitations for detection of tumors in dense breast tissue. Hence researchers are evaluating

role of blood-borne tumor markers like CA125, CA15-3, plasminogen activator inhibitor I, HSP90A, insulin-like growth factor binding protein 3, carcinoembryonic antigen (CEA) and CA27-29 as predictor of breast cancer. Kazarian et al observed CA15-3, PAI-1 and HSP90A as potential early prognostic markers, but not useful for accurate prediction of breast and there by not useful for screening purpose [50].

Eligibility of women for chemoprevention gets largely affected by risk assessment tools. Current methods of risk evaluation may miss some population as per the race/ ethnicity. Recently Gail model incorporated Women's Contraceptive and Reproductive Experience (CARE) model and Asian American Breast Cancer Study (AABCS) models to estimate more sensitive variables for Non-Hispanic and Asian American women respectively [51,52]. Gail's risk score of at least 1.66% at 5 years is the appropriate parameter to decide favorable risk/ benefit ratio. Decision on accepting chemopreventive therapy is very crucial. Tamoxifen and raloxifene are the drugs protective against ER positive breast cancers. But their use is associated with increased risk for endometrial cancer, thromboembolic events and vasomotor adverse effects. Their use depends on status of menopause. This makes the decision complex about whether to offer these agents in high risk women. Novel interventions but with less side effects should be studied in prospective population based trials.

Several challenges have been addressed by researchers for finding out the exact role of chemoprevention in reducing burden of the disease. Along with reduction in risk, one must study the effect of chemoprevention on mortality from the disease. Relatively, chemoprevention is a new field for research. It would be a rational and appealing preventive strategy for high-risk women. Randomized clinical trials of antie-strogens for chemoprevention have not demonstrated any benefit on the survival. Second important need is to develop drugs with good safety profile and strongest protective effect to target women with high-risk for breast cancer. The issue with the pharmacological breast cancer prevention trials is whether there is true prevention of clinically significant, life-threatening breast cancers, early treatment of tumours over diagnosed by intrinsic screening programs, or some mixture of the two. The consistent finding of protective effect of chemoprevention therapy on hormone-receptor-positive tumours supports the prediction made by modelling data that pharmacological prevention of breast cancer is actually early treatment of existent subclinical tumours [53].

Several societies and organizations endorsed the use of chemoprevention for primary prevention of breast cancer, but this modality of preventive intervention is under utilized in high-risk women also. There is lack of knowledge and awareness about risk assessment, calculation of lifetime or 5-year risk and use of chemoprevention among high-risk women. Also there may be concern of side effects during such preventive intervention. This might be a major contributor for poor uptake of chemoprevention agents among high-risk individuals [54]. Because of continued widespread prevalence of breast cancer, risk assessment and

implementation of preventive strategy especially in women at high risk should be a high priority in the health care sector. Breast surgeons and medical oncologists should be involved in preventive breast cancer units. To define breast cancer risk, one should have thorough knowledge of individual risk factor associated with breast cancer. The relative risk reduction depends on the risk factors and one should balance the management of risk factors against the potential harms with different pharmacological agents.

13. Conclusion

The approach to management of women at high risk for breast cancer is complex. It needs to understand risk and benefits of all types of interventional modalities at individual level of risk. First line of preventive therapy should be to encourage adoption of healthy lifestyle. It includes improved physical activity, reduction in body weight, adoption of healthy dietary pattern, avoidance of smoking, alcohol and use of hormonal preparations. Modifiable risk factors associated with breast cancer are lifestyle behavior and exogenous hormone therapy that should be targeted by counseling the women at risk. Non-modifiable risk factors include age; positive family history and reproductive factors that are associated independently with breast cancer. Counseling should follow appropriate screening of asymptomatic individuals who have modifiable risk factors and intervention is a cost-effective way to reduce future burden of the disease. Regular screening with mammography is one of the commonest and most popular screening tools for breast cancer.

Physicians should create awareness about identification of risk factors for breast cancer, screening tools and preventive strategy at public health level. Health care providers should support high-risk women with effective communication, counseling and imparting knowledge about risk/benefit ratio of chemoprevention to increase uptake and compliance for the preventive strategy. Breast cancer risk assessment tools and step-wise approach of providing chemoprevention to high-risk women will reduce the incidence of breast cancer.

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