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RESEARCH ARTICLE

RISK REDUCTION MASTECTOMY A NEW STRATEGY FOR PRIMARY AND SECONDARY PREVENTION OF BREAST CANCER– A LITERATURE REVIEW.

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Abstract

Background: In the last decade there has been a marked increase in the number of women requiring risk reduction mastectomy either before the development of breast cancer in high risk population or following the diagnosis of unilateral breast cancer. The breast surgeon and the oncologist are usually faced with difficult questions regarding the impact and the outcome of the various strategies that are used for risk reduction. This includes prophylactic mastectomy, close surveillance programs or chemoprevention. The outcome of these strategies and their effects on disease relapse and survival particularly prophylactic mastectomy either bilateral risk reduction mastectomy (brrm) for primary prevention or contralateral risk reduction mastectomy (crrm) for secondary prevention remains challenging and an area of great interest.

Methods and data sources: a narrative literature review was performed using the available electronic database. This was intended to assess the available tools for risk assessment in addition to the impact of prophylactic mastectomy (bilateral in high risk individuals or contra-lateral in unilateral breast cancer patients) on the following:

1. Breast cancer risk reduction & outcome.
2. Decision making process in women at a high risk for bilateral or contralateral breast cancer.
3. Patients satisfaction and psychological status after surgery.

Conclusion: Risk reduction prophylactic mastectomy in the form of bilateral or contralateral mastectomy is considered one useful strategy in patients at a high risk of breast cancer or with patients with unilateral breast cancer respectively. This strategy is recommended in some national and international guidelines.

Introduction:-

Prophylactic mastectomy is defined as the removal of the breast in the absence of malignant disease. The aim is to reduce the risk of breast cancer occurrence either for primary or secondary prevention strategy **(1).**

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Prophylactic mastectomy (PM) may be considered for women thought to be at a high risk for developing breast cancer, either due to a strong family history or in the presence of lobular carcinoma in situ or in known cases with BRCA1 or BRCA2 mutation or for those with TP53 (Li Fraumeni Syndrome), PTEN (Cowden syndrome, Bannayan-Riely-Ruvalcaba syndrome), CDHI, and STK11 or in those with a lifetime risk 20% or greater using risk assessment tools or in those patients who received radiation therapy to the chest between 10 and 30 years of age or finally in those with extensive mammographic abnormalities (extensive calcifications) where adequate biopsy or excision is impossible **(2)**.Annex (1) & (2).

To be mentioned, Prophylactic mastectomy is generally considered investigational for other indications including but not limited to contralateral prophylactic mastectomy in women with breast cancer without any high risk criteria **(3)**.LCIS is both a risk factor for breast cancer, including unilateral or bilateral cancer, and in some cases, it is a precursor for invasive lobular cancer.For those who develop invasive cancer, up to 35% may have bilateral cancer. Therefore, bilateral PM may be performed to eliminate the risk for development of breast cancer on the other hand; chemoprevention surveillance or oopheractomy are alternative risk reduction strategies. PMs are typically bilateral but can also describe a unilateral mastectomy as in patients who have previously undergone or are currently undergoing mastectomy in the opposite/contralateral breast for an invasive cancer (i.e.,CPM). The use of CPM has risen in recent years in the United States. An analysis of data from the National Cancer Data Base found that the rate of CPM in women diagnosed with unilateral stage I-III breast cancer increased from approximately 4% in 1998 to 9.4% in 2002 **(4,5)**.

The discussion for PM is a complicated one. It includes risk-benefit analysis with estimation of the patient's risk of breast cancer, typically based on the patient's family history of breast cancer and other factors as well. Several models are available to assess the risk, this includes the Claus model, Gail and BRCAPRO models. Breast cancer history in first- and second-degree relatives is used to estimate breast cancer risk in the Claus model. The Gail model uses the following 5 risk factors: age at evaluation, age at menarche, age at first live birth, number of breast biopsies, and number of first-degree relatives with breast cancer. BRCAPRO considers hereditary and pathologic factors as well . Moreover, the choice of PM is based on patient tolerance for risk, consideration of changes to appearance and need for additional cosmetic surgery, and the risk reduction offered by PM versus other options **(6,7)**. There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but most of them are based primarily on family history **(8,9)**. Figure 1, 2.However, some known individual risk factors confer a high risk by themselves. Annexure (3). See table 1 for more details.

a)	Lobular carcinoma in situ or
b)	A known BRCA1 or BRCA2 mutation or
c)	Another gene mutation associated with high risk, e.g., TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), CDH1, and STK11 or
d)	High risk (lifetime risk about 20% or greater) of developing breast cancer as identified by models that are largely defined by family history or
e)	Received radiotherapy to the chest between 10 and 30 years of age.

Table 1: List of factors known to indicate a high risk of breast cancer

A number of other factors may increase the risk of breast cancer but do not by themselves indicate high risk. It is possible that combinations of these factors may be indicative of high risk, but it is not possible to give quantitative estimates of risk. As a result, it may be necessary to individualize the estimate of risk, taking into account there numerous risk factors **(10)**.

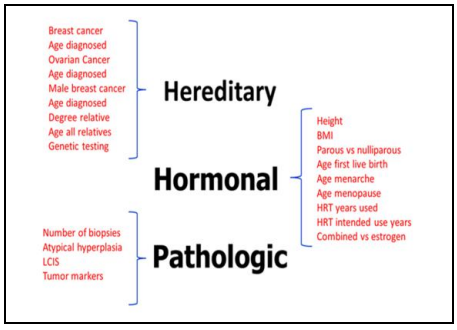

Fig. 1: Classification of breast cancer Risk Factors

Surgical options for prophylactic mastectomy include subcutaneous mastectomy (Skins or nipple sparing mastectomy) or total mastectomy, usually followed by breast reconstruction. Subcutaneous mastectomy is performed via an inframammary incision through which the breast tissue is resected, sparring the nipple-areolar complex. Historically, subcutaneous mastectomy was performed more commonly than total mastectomy, the latter procedure removes the majority of the breast tissue along with the nipple areolar complex through an elliptical skin incision. Given current nipple reconstruction techniques, total mastectomy is the preferred prophylactic procedure now a days. In both procedures a small amount of breast tissue is usaually left. This can develop into cancer later. The tissue left behind is usually in the axilla, inframammary fold, and skin flaps. This issue must be clearly explained to the patient, the physician should reiterate that the risk of breast cancer, therefore, cannot be completely eradicated with prophylactic mastectomy **(11,13)**.

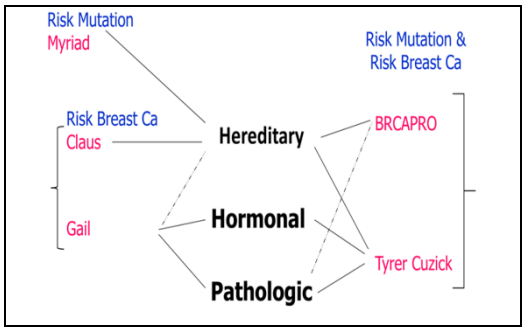

Fig. 2: Assessment tools for Breast Cancer Risk

This review article is destined to evaluate the role of BRRM; CRRM in general as well as the complication of PM, in addition to the Psychological impact of the procedure as well as the survival and follow-up program after the risk reduction mastectomy.

Methodology:-

In this article we reviewed the prevailing trends for using bilateral risk reduction mastectomy (BRRM) and unilateral risk reduction mastectomy (URRM) for primary and secondary prevention of breast cancer.

We electronically searched on PubMed, Medline, Medscape, Cochran, Health finder and Index databases of science Citations. Papers, bibliographies relevant studies published during the years of 2005 to 2015 are included in this review. The aim was to further define and clarify the following issues.

1. Current indicators for risk reeducation mastectomy prophylactic mastectomy (Bilateral or contralateral)
2. Risk assessment tools
3. Surgical techniques and its complications
4. Patient's satisfaction and psychosocial status after surgery
5. Outcome and survival results.

Discussion:-

Bilateral Risk Reduction Mastectomy (BRRM):-

Prophylactic mastectomy (PM) is generally considered for patients with a family history of breast cancer. The Assessment largely focused on a 1999 retrospective cohort analysis which concludes that approximately 13 moderate-risk women should undergo PM to prevent 1 cancer. Furthermore for women at high risk of breast cancer, the reduction in the incidence of breast cancer ranged from 90% to 94%. The author concluded that 4 to 8 high-risk women would need to proceed with PM to prevent 1 occurrence of breast cancer **(14)**.

A 2010 Cochrane review examined the impact of PM on mortality and other health outcomes. No Randomized controlled trials (RCTs) were identified. Thirty-nine observational studies with some methodological limitations were identified in the literature review. The studies presented data on 7384 women with a wide range of risk factors for breast cancer who underwent PM. Studies on the incidence of breast cancer and/or disease specific mortality reported risk reductions after bilateral PM, particularly for those with BRCA 1/2 mutations. The authors concluded that the available observational data suggested that bilateral PM reduces the rate of breast cancer mortality.

However, more rigorous studies (preferably RCTs) are still needed to confirm these findings; Furthermore, bilateral PM should only be considered among patients at very high risk of disease **(15)**.

In 2014, the National Comprehensive Cancer Network stated that PM should only be considered in high-risk women, defined as having a BRCA1 or BRCA2 mutation or another gene mutation associated with increased risk (e.g., PTEN, TP53, CDH1, STK11), a compelling family history. It may also be considered in women with lobular carcinoma in situ (LCIS) or prior thoracic radiotherapy before 30 years of age. Also it is advisable in patients with additional genetic mutations that have been associated with a high rate of cancer include TP53 (Li Fraumeni syndrome) and PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes) **(16)**. NB:In patients who received prior radiotherapy to the chest between the ages of 10 and 30 years of age, the increased risk of breast cancer can reach almost 30% by age 55 years. Patients with incidental LCI are considered at an increased risk for breast cancer.

Contralateral Risk Reduction Mastectomy (CRRM):-

The potential impact of CPM on survival is related to its association with a reduced risk of subsequent primary breast cancer in the other breast (i.e., contralateral breast cancer [CBC]). The U.S. Surveillance, Epidemiology and End Results (SEER) database, annual rates of CBC were stable between 1975 and 1985, later on the rates declined about 3% per year. In 1990, the annual decline in CBC rates was seen in women with estrogen receptor–positive cancer, with no decrease in those with estrogen receptor–negative cancer. The investigators suggested that the decrease in CBC rates in estrogen receptor–positive cancer may be attributed in part to the wide use in adjuvant hormone therapies **(17)**.

Molina-Montes et al published a systematic review on the risk of a second primary breast cancer in women with and without BRCA1 or BRCA2 mutations. Twenty studies were included; 12 retrospective cohort studies, 2 prospective cohort studies, and 6 case-control studies. The majority of studies included only women who had undergone genetic testing. A meta-analysis reported that the cumulative risk of a second primary breast cancer at 5 years after initial diagnosis was 14% (95% CI, 9% to 19%) in BRCA1 or BRCA2 mutation carriers and 3% (95% CI, 2% to 5%) in noncarriers. The Cumulative risks of a second primary cancer at 10 years after initial diagnosis was 22% (95% CI, 18% to 27%) in BRCA1 or BRCA2 mutation carriers and 5% (95% CI, 3% to 7%) in non-carriers **(18)**.

Complications of Prophylactic Mastectomy:-

Surgical Complications:

Surgical Complications following prophylactic mastectomy may be immediate or delayed. Gabriel et al. reported a 5-year complication rate of 30% in 92 women undergoing prophylactic mastectomy and implant reconstruction. Immediate complications included necrosis of the skin, nipple-areolar complex (with subcutaneous mastectomy), infection, wound dehiscence, hematoma or seroma, and pain. Later complications include capsular contracture, implant rupture or leakage, asymmetry or unsatisfactory cosmetic outcome, and lack of sensitivity of the overlying skin **(19)**.

Zion et al reported the experience of women who underwent prophylactic mastectomy and reconstruction with implants at the Mayo Clinic and subsequently required reoperation. Of 592 women who had bilateral prophylactic mastectomy and implant reconstruction, 52% required reoperation over a median follow-up of 14.2 years; 95% of these women had subcutaneous mastectomy. They also studied 502 women with a personal and family history of breast cancer who had undergone contralateral prophylactic mastectomy and reconstruction with implants along with therapeutic mastectomy for the affected breast. In this group, 39% required reoperation over a median follow-up of 8.8 years; 62% had subcutaneous mastectomy, and 38% underwent a total mastectomy. The Indications for reoperation were as follows. (a) Implant-related concerns (50% to 60%) includes, implant rupture or leakage or capsular contracture nodule excision (4% to 10%). (b) Non-implant-related aesthetic concerns (15% to 23%) like, revision of the scar or nipple-areolar revision **(20)**.

In 2015, Silva et al published a large multicenter study including 20,501 women with unilateral breast cancer from the American College of Surgeons National Surgery Quality Improvement Program (NSQIP) database. A total of 13,268 (64.7%) women underwent unilateral mastectomy and 7233 (35.3%) had bilateral mastectomy. The analysis did not report on high-risk factors such as BRCA mutation status or family history. All women had breast reconstruction; a higher proportion of women who had unilateral mastectomy (19.5%) than bilateral mastectomy (8.9%) had autologous reconstruction; the remainder had implant-based reconstruction. The authors conducted analyses controlling for confounding variables (i.e. age, race smoking, diabetes, chronic pulmonary disease,

hypertension) and stratifying by type of implant. The rate of overall complications was significantly higher for women who had a bilateral versus unilateral mastectomy, regardless of reconstruction type. Among women with implant reconstructions, overall complication rates were 10.1% after bilateral mastectomy and 8.8% after unilateral mastectomy (adjusted odd ratio [OR], 1.20; 95% CI, 1.08 to 1.33). In women with autologous reconstructions, overall complication rates were 21.2% after bilateral mastectomy and 14.7% after unilateral mastectomy (adjusted OR=1.60; 95% CI, 1.28 to 1.99). The most common complication was reoperation within 30 days, followed by surgical site complications. Transfusion rates were also significantly higher ($p<0.001$) in women with bilateral versus unilateral mastectomies who had either type of reconstruction. The rates of medical complications were relatively low approximately 1% of women who had implant reconstructions and 3% of women who had autologous reconstructions experienced a medical complication (ie, pneumonia, renal insufficiency or failure, sepsis, urinary tract infection, venous thromboembolism) and did not differ significantly for unilateral versus bilateral mastectomies. Several single-center studies have also found significantly higher surgical complication rates after bilateral than unilateral mastectomy **(21)**.

Miller et al, in 2013 included 600 women with unilateral breast cancer, CPM remained associated with a significantly higher risk of any complication (OR=1.53; 95% CI, 1.04 to 2.25) and a significantly higher risk of major complications (OR=2.66; 95% CI, 1.37 to 5.19) than unilateral mastectomy. Eck et al in 2014 assessed 352 women with unilateral breast cancer, 94 (27%) women had complications, 48 (14%) in the unilateral mastectomy group and 46 (13%) in the bilateral mastectomy group.(15) The difference between groups was not statistically significant ($p=0.11$), but this study may have been underpowered. They found a significant delay in adjuvant therapy after surgical complications. Women with complications waited longer before receiving adjuvant therapy than those without complications (49 days vs. 40 days, $p<0.001$) **(22)**.

Psychosocial Issues:-

In the literature, there are lots of accumulating data reported by questionnaire, Frost et al assessed long-term satisfaction as well as psychological and social function in 572 of 609 women (94% participation) with a family history of breast cancer following bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. Family history of breast cancer was the most commonly cited reason for prophylactic mastectomy. The most frequent combination of reasons was family history, physician advice, and nodular breasts **(23)**.

In the study, 74% of the women reported a diminished level of emotional concern regarding the development of breast cancer. The majority of women reported no change or even favorable response in regarding their emotional stability, degree of stress, self-esteem, sexual relationships, and feelings of femininity. However, 36% were unsatisfied with their body appearance after prophylactic mastectomy. The degree of satisfaction after prophylactic mastectomy was assessed by the following; body appearance, level of stress, implant-related problems, and the need for reconstruction after prophylactic mastectomy. To be mentioned the physician's advice as the primary reason for undergoing prophylactic mastectomy was associated with dissatisfaction. Stefanek et al. reported, it was found that cancer-related worry, prior breast biopsies, and subjective risk estimates were the most significant variables in the group undergoing prophylactic mastectomy. Women completing the procedure with strong support from families and friends (and those following formal risk counseling) were most satisfied with their decision **(24)**

Hatcher et al. in a prospective trial studied the psychosocial impact of bilateral prophylactic mastectomy through questionnaires and semi structured interviews. He assessed 143 women at increased risk of breast cancer who were offered bilateral prophylactic mastectomy. (79 women) accepted, (64 women) declined, and 11 others deferred making a decision. Follow-up interviews were conducted at 6 and 18 months. Psychological morbidity and anxiety were high before surgery and decreased significantly after surgery in the group that underwent a bilateral prophylactic mastectomy. On the other hand, it remained high in the group that opted for regular surveillance. The researchers noted that women who chose surgery were more likely to have undergone prior breast biopsies or genetic testing. After surgery, these women maintained a positive body image and reported few or no changes in sexual function. Furthermore, women who chose prophylactic mastectomy strongly believed that the procedure would significantly reduce their chances of developing breast cancer. Generally, the acceptors tended to report higher lifetime risks of developing the disease than the decliners. Hatcher et al. stressed on the importance of Genetic counseling. They reiterate that it is mandatory prior to making any decision regarding prophylactic mastectomy. This is to ensure accurate risk assessment and to inform the audience about their risk **(25)**.

Survival:-

Bilateral Risk Reduction Mastectomy:-

Mayo Clinic Study—In an effort to quantify the risk reduction associated with prophylactic mastectomy, Hartmann et al. at the Mayo Clinic performed a retrospective cohort analysis of 639 women with a family history of breast cancer who had undergone prophylactic mastectomy between 1960 and 1993. Women were assigned retrospectively to either a moderate-risk group (425 women) or high-risk group (214 women) based on the extent of their family history of breast cancer. Follow-up was available for 99% of the cohort for a minimum of 2 years; median follow-up was 14 years (9,095 person-years). The investigators compared the total number of breast cancers observed among study participants with the total number predicted by the Gail model (for the moderate-risk group) and by a nested sister control study (for the high-risk group). The Gail model predicted that 37.4 women in the moderate-risk group would develop breast cancer by the median follow-up of 14 years. In the studyr, only four of these women developed the disease, representing an 89.5% reduction ($P < .00001$) in incidence following prophylactic mastectomy. The Gail model also predicted that 10.4 women in the moderate-risk group would die of breast cancer, but, in fact, no deaths from breast cancer occurred in these women **(26)**.

Regarding the high-risk group, 3 of the 214 women developed breast cancer after prophylactic mastectomy. From their sisters' experiences, 30 breast cancers were predicted in these high-risk women. Thus, prophylactic mastectomy was associated with a 90% reduction in the risk of breast cancer in high-risk women. Similarly, compared with the expected number of breast cancer deaths, prophylactic mastectomy in the high-risk group resulted in an 81% to 94% reduction in breast cancer mortality.

Dutch Study— This is a prospective study that evaluated 139 BRCA1 or BRCA2 carriers. All women were followed at the Rotterdam Family Cancer Clinic. None had a history of breast cancer. A total of 76 of these women accepted to undergo prophylactic mastectomy, and 63 remained under close surveillance. The mean follow-up was 2.9 ± 1.4 years. No cases of breast cancer were observed in the prophylactic mastectomy group, compared to eight cases in the surveillance group (hazard ratio: 0; 95% confidence interval [CI]: 0-0.36). Out off the eight cases, four were interval cancers diagnosed between scheduled screening tests. Four of the cancers spreaded to the axillary lymph nodes, Seven were estrogen-receptor and progesterone-receptor negative. The interval from initiation of surveillance to the diagnosis of cancer ranged from 2 to 42 months. The researchers concluded that in women with a BRCA1 or BRCA2 mutation, at 3 years of follow-up, prophylactic bilateral total mastectomy reduced the incidence of breast cancer with a relative risk reduction of 100%, (absolute risk reduction of 12.7%) **(27)**.

Contralateral Risk Reduction Mastectomy:-

A systematic review and meta-analysis of studies on CPM was published in 2014 by Fayanju et al. The authors searched for published studies that compared the incidence of CBC in women with unilateral disease who did and did not undergo CPM. Fourteen observational studies met eligibility criteria and were included in the meta analysis. In a meta-analysis of 4 studies, mortality from breast cancer was lower in the group that had CPM (relative risk [RR], 0.69; 95% CI, 0.56 to 0.85). Moreover, in a meta-analysis of data from 6 studies, overall survival (OS) was significantly higher in patients who underwent CPM (n=10,666) than those who had no CPM (n=145,490) (RR=1.09; 95% CI, 1.06 to 1.11). The authors also conducted a subgroup analysis by risk level in which all patients were BRCA mutation carriers and studies in which all patients had a family history of breast cancer (4 studies). Those were categorized as indicating higher familial/genetic risk. Together, the studies included 618 patients who had CPM and 1318 patients who did not. In a meta-analysis limited to these 4 studies, neither OS nor mortality from breast cancer differed significantly among women who had or did not have CPM. The relative risk of breast cancer mortality with and without CPM was 0.66 (95% CI, 0.27 to 1.64). Regarding the OS with and without CPM, the relative risk was 1.09 (95% CI, 0.97 to 1.24). The absolute reduction in the risk of metachronous breast cancer did not differ in women with and without CPM when data from all 8 studies were analyzed (risk difference [RD], -18.0%; 95% CI, -42.0% to 5.9%, but was significantly lower in women with CPM in the 4 studies exclusively enrolling women at increased familial/genetic risk (RD = -24.0%; 95% CI, -35.6% to - 12.4%). The authors stated that the improvement in survival after CPM in the general breast cancer population was likely not due to a decreased incidence of contralateral breast cancer, but rather was secondary to selection bias (as CPM recipients may be otherwise healthier and have better access to health care than the other group who declined the procedure **(28)**.

Kruper et al in a large dataset from the SEER database in 2014 studied CBC and survival outcomes. The investigators conducted a case-control analysis including 28,015 CPM patients and 28,015 unilateral mastectomy patients, matched on age group, race/ethnicity, extent of surgery, tumor grade, tumor classification, node

classification, estrogen receptor status, and propensity score. The investigators were not able to match for BRCA or other mutation status. When all matched patients were included, disease-specific survival (DSS) and OS were significantly lower in women who underwent unilateral mastectomy compared with CPM. For DSS, the hazard ratio (HR) was 0.83 (95% CI, 0.77 to 0.90); for OS, it was 0.77 (95% CI, 0.73 to 0.82). Presumably, CPM would increase survival by lowering the risk of CBC. The authors conducted another analysis excluding women diagnosed with CBC; the remaining sample was still large (25,924 women with unilateral mastectomy and 26,299 women with CPM). In the analysis excluding women with CBC, DSS and OS remained significantly lower in women who had unilateral mastectomy versus CPM. For DSS, the HR was 0.87 (95% CI, 0.80 to 0.94); for OS, it was 0.76 (95% CI, 0.71 to 0.81). The investigators suggested that the survival benefits found in CBC patients was not due to prevention of CBC, but instead to selection bias (e.g., healthier women choosing CBC). A limitation of the analysis was the inability to control for risk factors including gene mutation status, family history, and a history of radiotherapy to the chest between ages 10 and 30 years **(29)**. In 2013, Yao et al evaluated OS after CPM by analyzing data from the National Cancer Data Base. The data were collected from 1450 Commission of Cancer–accredited cancer programs. The analysis included 219,983 women who had mastectomy for unilateral breast cancer; 14,994 (7%) of these women underwent CPM at the time of their mastectomy. The investigators did not report risk factors such as known genetic mutations. The 5-year OS rate was 80%. In an analysis adjusting for confounding factors, the risk of death was significantly lower in women who had CPM than in women who did not. The adjusted HR for OS was 0.88 (95% CI, 0.83 to 0.93). The absolute risk of death over 5 years with CPM was 2.0% lower than without CPM. In a subgroup analyses, there was a survival benefit after CPM for individuals aged 18 to 49 years and aged 50 to 69 years, but not for those 70 years or older. There was also a survival benefit for women with stage I and II tumors, but not for stage III tumors. Pesce et al. in 2014, focused on the subgroup of patients who were young (with stage I or II breast cancer. A total of 4338 (29.7%) of 14,627 women in this subgroup had CPM at the time of mastectomy. Median follow-up was 6.1 years. In a multivariate analysis controlling for potentially confounding factors, OS did not differ significantly among patients who underwent unilateral mastectomy and those who also had CPM (HR=0.93; 95% CI, 0.79 to 1.09). Moreover, among women younger than 45 years with estrogen receptor–negative cancer, there was no significant improvement in OS in those who had CPM versus unilateral mastectomy (HR=1.13; 95% CI, 0.90 to 1.42) **(30)**.

Follow-up after Prophylactic Mastectomy:-It is very important to mention that Prophylactic mastectomy does not completely eliminate the risk of subsequent breast cancer. Hence, it is mandatory that women treated with this procedure undergo long-term follow-up, perform regular, monthly examination of the chest wall, and undergo annual clinical examination. Annual mammography should be strongly considered in women who have had subcutaneous mastectomy. This has been an area of controversy. Those in favor stress that the residual breast tissue warrants a thorough clinical and radiologic assessment to enable early detection of malignancy. However, those against annual mammography believe that the thin layer of the residual breast tissue can be easily palpated on clinical examination of the chest wall and that annual mammography does not provide any additional benefit **(31)**.

In Summary:-

The following are the current practice guidelines and position statements to be taken in to consideration.

1. **National Comprehensive Cancer Network (NCCN 2016) :**"Risk-reduction mastectomy should generally be considered only in women with a genetic mutation conferring a high risk history for breast cancer, compelling family history, or possibly with LCIS [lobular carcinoma in situs] or prior thoracic radiation therapy at < 30 years of age. The value of risk-reduction mastectomy in women with deleterious mutations in other genes associated with a 2-fold or greater risk for breast cancer (based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown."The guideline states: "the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer, psychological and social issues of bilateral mastectomy, and the risks of contra lateral mastectomy. The use of a prophylactic contralateral mastectomy to a breast treated with breast-conserving therapy is very strongly discouraged." Genes that confer more than 20% risk of breast cancer include BRAC1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and TP53 **(32)**.

2. **Society of Surgical Oncology (SSO) 2007 :**The Society of Surgical Oncology developed a position statement on PM in 1993 and updated it in 2007.The position statement states that bilateral PM is potentially indicated in patients with: Known BRCA 1 or 2 mutations or other genes that strongly predispose susceptibility to breast cancer,A history of multiple first-degree relatives with breast cancer history or multiple successive generations of breast and/or ovarian cancer, or Biopsy-confirmed, high-risk histology such as atypical ductal or lobular hyperplasia or LCIS. The position statement also stated that CPM may be potentially indicated in patients: With

high risk (as previously defined) of contralateral breast cancer, In whom surveillance would be difficult such as with dense breast tissue or diffuse indeterminate microcalcifications, or to improve symmetry **(33)**.

3. **National Cancer Institute (NCI) 2012:**The fact sheet of NCI, issued in 2012 provided the following information: "Prophylactic surgery to remove both breasts (called bilateral prophylactic mastectomy) can reduce the risk of breast cancer in women who have a strong family history of breast and/or ovarian cancer, who have a deleterious (disease-causing) mutation in the BRCA1 gene or the BRCA2 gene, or who have certain breast cancer-associated mutations in other genes, such as TP53 and PTEN." **(34)**

Conclusion:-

Bilateral & contralateral risk reduction mastectomy is one risk reduction measure for patients at a high risk of breast cancer or contralateral cancer respectively.Accurate risk assessment by a trained genetic counselor is an obligatory first step, as many women overestimate their risk of breast cancer. It is a highly personal decision that must, therefore, be preceded by an in-depth discussion with the patient by a multidisciplinary team regarding the benefits of the procedure vs the potential surgical and psychological risks. In addition, it is imperative that these women be informed of alternative management options, including chemoprevention, increased surveillance, and prophylactic cophorectomy.

Annex (1) : The following personal and/or family characteristics suggest a high-risk individual who would be a candidate for genetic testing:

a. Age onset of breast cancer ≤50
b. Triple negative tumor (ER-PR-HER2-) and age ≤60
c. Ashkenazi Jewish heritage and breast cancer any age
d. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric)
e. First-degree relative with breast cancer age ≤50
f. Two relatives on the same side of the family with breast cancer and/or pancreatic cancer
g. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
h. Male Breast Cancer
i. Known mutation carrier in the family

Annex (2):-Patients without a personal history of Breast Cancer: Patients should be made aware that testing an affected relative first when available can be more informative than testing themselves since a negative result will not give them more insight into their family history. If an affected relative is not available, patients should be reminded of the limitations of testing. Ideally, a three-generation pedigree including maternal and paternal lineage should be obtained. This information can be used to guide the type of testing to be performed and the selection of patients who may benefit from further counseling with a CGC. Patients without a personal history of breast cancer meet criteria for genetic testing if they have the following history:

a) First-or second-degree relative with early age onset of breast cancer ≤45.
b) Ashkenazi Jewish heritage and family history of breast cancer any age
c) Two or primary breast cancers (cancers can be asynchronous, synchronous, bilateral or multicentric) in a single family member
d) Two or more relatives on the same side of the family with breast cancer and/or pancreatic cancer
e) Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
f) Male Breast Cancer
g) Known mutation carrier in the family

Annex (3):-Risk Assessment Tools

In addition to National Comprehensive Cancer Network (NCCN) guidelines for identifying patients appropriate for genetic testing, there are numerous models and online calculators available to predict the likelihood of carrying a BRCA1 or BRCA2 mutation based on family and personal history. In general, patients with a 5-10% or greater likelihood of carrying one of these genes should be recommended to considered for testing and/or genetic counseling.

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The authors report no conflict of interest in this work.

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