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RESEARCH ARTICLE

STRATEGIES TO COMBAT THE RISING INCIDENCE OF BREAST CANCER

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ABSTRACT

Breast cancer is now the most prevalent form of cancer in Indian women. The Incidence of Breast Cancer in India is 25.8 per 100,000 women, while in a developed country such as the United States of America, it is 124 per 100,000 women. The 5-year survival in India is however only 50% while in the USA, it is 91%. The prevalence of breast cancer is increasing in India, especially in the younger age. Significant factors for developing Breast cancer are dietary habits, lifestyle, reproductive pattern, and usage of post-menopausal hormonal therapy. In a resource limited country with a large population like India, a National program combining prevention strategies, educational programs for early detection will have the best chance of substantially lowering the incidence and mortality from this lethal disease. A collaborative approach of government, non-government organizations, and the people at large has the potential to substantially reduced the incidence and mortality from breast cancer. We briefly summarize the data on the incidence, risk factors, and risk reduction approaches for achieving this goal.

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INTRODUCTION

Every year, more than a million females globally are diagnosed with breast cancer (Malvia, 2018). In advanced countries, the mortality rate of females with breast cancer is low, while in emerging nations such as India, most females with breast cancer will die from it (Noor *et al.*, 2016). In India, breast cancer incidence is rising (Malvia, 2018). Breast cancer is potentially a preventable illness. Additionally, if it is detected early, it is highly curable with less intense treatments. This would be an ideal strategy for a country like India to maximize the benefits with the lowest of expense. We present herein the incidence, etiological factors, assessment of risk, and risk reduction approaches.

Breast Cancer Incidence in India: The incidence of Breast cancer in India is 25.8 per 100,000 women (Malvia, 2018), however it varies widely across the country. According to a study conducted by Malvia *et al.*, the incidence rate in Delhi is 41 per 100,000 followed by Chennai's 37.9 per 100,000, Bengaluru 34.4 per 100,000 and Thiruvananthapuram which has an incidence rate of 33.7 per 100,000¹. Reports also suggest that the mortality rate of Breast cancer in India is 12.7 when compared to 17.1 in the USA (Malvia, 2018). However, Incidence of Breast Cancer in India is only 25.8 per 100,000 women while in a developed country such as the

United States of America it is 124 per 100,000 women (Malvia, 2018). Hence the conclusion despite a lower incidence rate in India, the mortality rate is very high.

Breast Cancer: Risk Factors: Multiple studies have been carried out mostly in western countries to understand the causes of breast cancer (Incidence: North American Association of Central Cancer Registries, 2018; Noor, 2016). Large epidemiological studies focused on migrant populations reveal that genetic factors have a smaller role, while lifestyle plays a major role in increasing the incidence of breast cancer (Chaturvedi *et al.*; Ziegler, 1993). People migrating from low incidence areas to high incidence area acquires the same risks as the native population they migrated to (Ziegler, 1993). This data strongly supports the role of socioeconomic and other lifestyle changes as the significant drivers of breast cancer risk.

Reproductive Factors

Age at onset of cycles: The risk of developing breast cancer is higher in females who start their cycles before the age of 12 years, as compared to those who start later (Kelsey, 1993). The increased risk is noticeable in both pre- and postmenopausal breast cancer (Velle, 2006).

Age at Cessation of Menses: Women with natural menopause at the age of 55 years have 30% more chance of getting Breast Cancer when compared to women who have Bilateral oophorectomy before the age of 45 years (Trichopoulos, 1972). It is projected that there would be a 3% increase for every year

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delay after the age of 45 to age at menopause (Trichopoulos, 1972). The delay in menopause leads to prolonged exposure to endogenous hormones and continued ductal epithelium hyperplasia (Velle, 2006; Trichopoulos, 1972).

Duration and frequency of cycles: Reduced duration of each cycle may be associated with higher risk (Garland, 1998). According to some studies, conversely, longer duration between cycles, and irregular cycles seem to decrease the risk (Garland *et al.*, 1998). This phenomenon may be related to the duration of the luteal phase, where the levels of both estrogen and progesterone are elevated.

Parity: Full-term pregnancy before the age of 20 is linked to decreased risk of developing breast cancer (Haq, 2009; <https://www.cancer.net/cancer-types/breast-cancer/risk-factors-and-prevention>). This is likely due to the maturation of glandular epithelium of the mammary cells, that occurs in the first pregnancy (Russo *et al.*, 1982). Nulliparous women have a higher risk of breast cancer as compared to multiparous women (Russo *et al.*, 1982). Additionally, late first pregnancy increases the risk. Use of in-vitro fertilization which requires exogenous hormones administration to facilitate pregnancy may also increase the risk of breast cancer (Russo, 1982).

Spacing of parturition: The risk of developing Breast cancer is decreased with every childbirth. This is further magnified with each subsequent birth, especially if they are closely spaced (Rosner, 1994).

Lactation: Lactation appears to have a beneficial effect in reducing the risk of breast cancer. It is partly dependent on the duration and the number of children who are breastfed (Lane-Clayton, 1926; Romieu, 1996). The risk reduction appears to be 50 % for a female who breastfed each child for two years or more (Romieu, 1996; Heck, 1997).

Hormonal Supplements: Exposure to exogenous hormones as hormone replacement therapy leads to increased risk of breast cancer (March Banks, 2002). Soroush *et al.* report that oral contraceptives do not contribute to breast cancer risk, except when used in teenage years (Soroush *et al.*, 2016).

Genetic Factors: Only a minority of breast cancers are driven by genetic mutation. In the developed countries of the west such as the United States of America, BRCA-1 and BRCA-2 accounts for about 15% of all breast cancer (Keaneth Offit, 2006). These are the most frequently seen autosomal dominant oncogenes. Patients who Inherit them are at 25-80% risk of developing breast cancer (Godet, 2017; Somasundaram, 2010). In India, very limited number of studies have been done on BRCA-1 and BRCA-2 gene mutation incidence.

Non-Hormonal Factors

Diet and Exercise: One of the lifestyle factors which have been studied extensively is the influence of diet on the risk of breast cancer (Hoskins, 1995). The women who gain weight in the middle age years have an increased risk of breast cancer (McTierman, 2003; Holmes). Additionally, maintaining one's weight or losing weight also decreases the risk of breast cancer (Holmes).

History of Evolution of Breast Cancer: The present breast cancer growth hypothesis suggests that duct cell develops

hyperplasia that transforms into atypical hyperplasia, progressing further to in situ cancer, and lastly invasive cancer (Alfred, 2000). Cancer becomes clinically noticeable at 1 cm and radio graphically at 1 mm (Constance, 2005). The transition from an ordinary cell to the clinically noticeable cancer requires many years. This long duration gives us many chances to stop this progression and prevent the development of the invasive disease (Alfred, 2000).

Risk Assessment: The first step in determining appropriate risk reduction is the assessments of the risk. Ideally prevention measures should be tailored based on individual's risk. There are two most commonly used models to determine the risk of an individual. The Gail model was developed from the data of US cancer registries, and it incorporates age, previous breast biopsy age at first live birth, first degree relative with breast cancer, and atypical hyperplasia on any previous breast biopsy (Gail, 1989; Augustine *et al.*, 2015). The Gail model does not give adequate significance to family history. The other model which is available, is the Claus model which factors family history in evaluating an individual's risk for breast cancer (Claus, 1993). One could use the Claus model when there is a family history of breast cancer, or in the absence of family history, Gail model could be used (Augustine, 2015; Claus, 1993).

Disease Prevention Strategies: The fact that breast cancer evolves gradually makes it possible to offer interventions at different stages. We have a decent understanding of the risk factors ranging from the hormonal, nutritional, and additional lifestyle factors (Haq, 2009). Appropriate interventions to lower the risk factors from diet, exercise, weight management, reproductive pattern, breast-feeding habits to medication and surgical procedure can all be used in an appropriate manner based on the risk of the individual. The first step of courses is risk assessment, especially for the individual who is at high risk of developing the disease. General measures of nutrition, exercise are applicable to all.

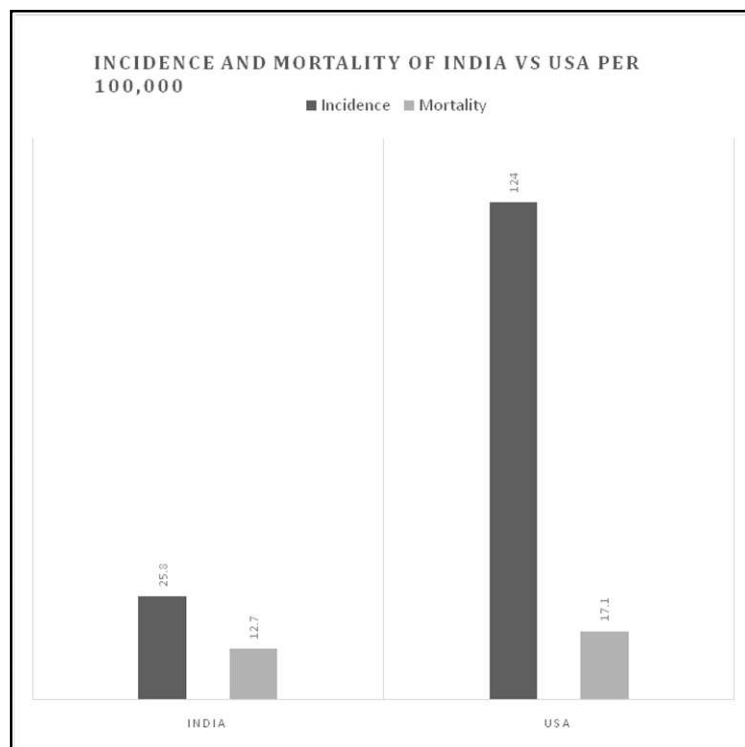
Manipulating natural hormonal pattern: *We know vigorous exercise starting at a young age delays the onset of menarche or leads to an anovulatory cycle which can decrease the risk of breast cancer* (Bernstein *et al.*, 1987). Early full-term pregnancy before the age of 20 reduces the risk, and this may not always be practical in the present-day society; however, lactation should be encouraged and practiced to decrease the risk. Avoiding post-menopausal hormonal therapy would also be beneficial in decreasing the risk (Rassouw *et al.*, 2002).

Diet: Multiple studies have evaluated the role of diet and specific dietary factors like fat (Haq, 2009). However, a consistent role of a specific diet has not been proven to reduce the risk of breast cancer. According to Chlebowski *et al.* the breast cancer risk is increased in women who had weight gain in the middle age years (Chlebowski, 2019). Avoiding the weight gain or reducing the weight decreases the risk (Chlebowski, 2019).

Medication for Risk Reduction: Raloxifene and tamoxifen are selective estrogen receptor modulators (SERM's) (Fisher *et al.*, 1998). They have shown to be effective in reducing the risk. These drugs reduced the risk by 38% They both are equally effective, but raloxifene is better tolerated and has lesser toxicity (Cummings *et al.*, 1999).

Table 1 summarizes the risk factors and proportionate risk.**Risk Factors for Breast Cancer (Table-1)**

RISK FACTORS	PROPORTIONATE RISK
HORMONAL	
Age at menarche (Less than 12 years vs. more than 15 years) ⁶	Breast cancer risk increases slightly for each year (by about 1.3%).
Age at menopause (Less than 45 years vs. more than 55 years) ⁶	Breast Cancer risk each year later, menopause increases (by about 3%).
Age at first live birth (Less than 18 years vs. more than 30 years or no live births) ⁶	Risk of Breast cancer is increased by 1.9% when the first live birth is after 30 years.
Combined hormone replacement therapy in postmenopausal (at least 5 years of use or current use vs. no use) ¹⁸	Increases the risk of breast cancer by 1.32 %, with higher risk associated with longer use.
NON-HORMONAL	
Family History	2 times higher risk for women with more than one first-degree relative affected.
Genetic Factor ²⁰	Account for 15% of all female breast cancers and 15%-20% of all familial breast cancers.
BMI ^{23,24}	Postmenopausal breast cancer risk is about 1.5 times higher in overweight women and about two times higher in obese women than in lean women

**Surgical approach:**

Total Mastectomy: Women with very high risk, especially with BRCA 1-2 mutation would benefit from prophylactic mastectomy (Meijers *et al.*).

Total Salpingo-Oophorectomy: An alternate surgical approach of bilateral salpingo oophorectomy, if performed at or before the age of 40 in women with a very high risk of breast cancer, including BRCA 1-2 reduces risk by 50%³⁵. It also reduces the risk of ovarian and fallopian tube cancer by 80 to 90% (Rebbeck, 2004).

Early detection strategies

Breast self-Examination: Breast self-examination, a simple measure though not proven to be beneficial in a randomized controlled trial, could still be of value in a country like India where patients frequently present with large masses.

Mammography: Mammography Is widely used in western countries and has reduced the mortality and also has led to early detection, where management is simpler and more effective (<https://www.cdc.gov/cancer/breast/pdf/BreastCancerScreeningGuidelines.pdf>). The current recommendation in the western world is, women age of 40-50 years should have annual mammography done and women age 50-74 once in two year (<https://www.cdc.gov/cancer/breast/pdf/BreastCancerScreeningGuidelines.pdf>). In India it may be difficult to recommend mammography for the entire country, however, urban women who are at higher risk should follow the guidelines recommended in the western countries (<https://www.cdc.gov/cancer/breast/pdf/BreastCancerScreeningGuidelines.pdf>).

Conclusion

Breast cancer is the leading cause of cancer-related death in women in India, the gradual nature of the development of

breast cancer means there is an adequate interval of time at various stages to prevent it or either detect it. For a nation like India with limited health care resources and a population over 1 billion, a concentrated effort by government, non-government agencies, and the community at large to use all the resources in applying prevention and risk reduction strategies, particularly exercises weight management and breastfeeding can substantially reduce the disease burden. Women who are at high risk should follow the appropriate guidelines.

Ethical Approval: It is not applicable in this review.

Consent: It is not applicable in this review.

Competing Interests: Author have declared that no competing interest exists concerning this review.

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