

Menopause Hormone Therapy in the Changing Trends of Breast Cancer in India

With a diverse geographical, cultural, and socioeconomic landscape, India exhibits heterogeneity in cancer incidence. Cancer of the breast from 19 population-based registries (PBCRs) and cervix uteri from 7 PBCRs were the most common cancers in women (updated 2020).^[1] Data show that cancer cervix is on the decline, reflecting the awareness created by promoting and implementing screening methods and introducing the human papillomavirus vaccination. There is a disturbing increase in breast cancer incidence, affecting younger, premenopausal women and disheartening survival rates.^[1] Twenty-five years ago, 69% of the patients were above 50 years of age; presently, almost 48% of patients are below 50 years of age.^[2] Breast cancers in the young are hormone positive in 48%; the rest are triple-negative breast cancers and more aggressive. A large segment of women present at stages three and four; hence, a rough estimate of survival is not even 60%, unlike 89% in the United States.^[3]

India, with a population of 1.2 billion people, about 96 million are women aged 45 years and above, and this number is projected to increase to 401 million in 2026.^[4] At present, the life expectancy of women in India is 70.3 years, which is expected to increase to 77 years by 2050 (World Health Organization, 2018). This group presents formidable future challenges to public and private health-care providers.

The estimated mean age of menopause is 46 years in India, which is lower than Caucasians. The available Indian data hypothesized that the early age of menopause predisposes a woman to chronic health disorders such as osteoporotic fractures, type 2 diabetes mellitus (T2DM) a decade earlier than a Caucasian woman. Breast cancer incidence peaks before the age of 50 years. In a multicenter, urban, hospital-based study conducted by the Indian Menopause Society, the incidence of vasomotor symptoms was 75%.^[5] These facts underline an urgent need to promote awareness and empower health-care professionals to manage midlife women.

Prescription of menopausal hormone therapy (MHT) appears to be a safe and an effective option for healthy, symptomatic women within 10 years of menopause or younger than age 60 years, who do not have contraindications to MHT and are at low risk for breast cancer. Prescription of MHT has to be individualised and we need to inform the woman about the absolute risk of breast cancer and the beneficial effects of MHT. There is reassuring data from the Women's Health Initiative

on the beneficial effects of menopausal hormone therapy (MHT) at menopause transition on bone, T2DM, lipids, and cardiovascular systems.^[6] Conjugated equine estrogen plus medroxyprogesterone compared with placebo among 16,608 women with a uterus was associated with statistically significantly higher breast cancer incidence with 584 cases (annualized rate, 0.45%) versus 447 cases (annualized rate, 0.36%; hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.13–1.45; $P < 0.001$) and no significant difference in breast cancer mortality with 71 deaths (annualized mortality rate, 0.045%) versus 53 deaths (annualized mortality rate, 0.035%; HR, 1.35; 95% CI, 0.94–1.95; $P = 0.11$). Long-term data on postmenopausal women with prior hysterectomy using conjugated equine estrogen alone compared with placebo among 10,739 women with a prior hysterectomy were associated with statistically significantly lower breast cancer incidence with 238 cases (annualized rate, 0.30%) versus 296 cases (annualized rate, 0.37%; HR, 0.78; 95% CI, 0.65–0.93; $P = 0.005$) and were associated with statistically significantly lower breast cancer mortality with 30 deaths (annualized mortality rate, 0.031%) versus 46 deaths (annualized mortality rate, 0.046%; HR, 0.60; 95% CI, 0.37–0.97; $P = 0.04$).^[7] These potential benefits of MHT may have a substantial impact at a population level.

A recent study published in *Lancet* by a collaborative group on hormonal factors in breast cancer is an individual participant meta-analysis of the worldwide epidemiological evidence on type and timing of menopausal hormonal therapy (MHT) and breast cancer risk. Like some epidemiological and observational studies, the *Lancet* study has shown an association between MHT and breast cancer use. Obesity is considered an independent risk factor for breast cancer; MHT did not have an adverse effect in obese postmenopausal women. This study has shown an association between obesity and breast cancer.^[8] Most observational data relating MHT with breast cancer risk exhibit risk ratios (odds ratio and relative risk) rarely exceeding 1.5, and virtually all associations reported as <2.0 , which may not have clinical impact. Moreover, the data include studies from the 1980.

There is a paucity of data regarding the use of MHT from India. One cannot neglect the symptomatic menopausal women for the presumed assumption of increased breast cancer risk; the data need to be

analyzed from a local risk perspective. A cautious approach is needed to prevent the misuse of MHT. To manage a woman at menopause, the physician needs to analyze the benefit–risk profile by assessing a patient’s baseline risk for chronic disorders such as hypertension, diabetes, venous thromboembolism, osteoporosis, and breast cancer. In this scenario, one needs to understand the term “individualization” of MHT. The prescription of the type, dose, and route depends on the woman’s profile and may change in an individual over a period of time. Safe use of MHT requires an annual follow-up and reassessment. The clinical implication of the available data is to advise women about the right choice of treatment for menopausal symptoms and assess the risk of developing breast cancer.

A thorough understanding of the effects of “menopausal hormone therapy (MHT)” on the breast is essential to all practitioners of menopause. The relation of MHT on the breast is complex, accelerates mitosis, or promotes apoptosis depending on the type, dose of MHT, and the milieu. Based on the randomized controlled trial’s casualty analysis, MHT may not initiate but potentiate the growth of hormone-receptor-positive breast cancers.^[9] The problem is the inability to diagnose women at the occult stage of the disease. Hence, it is prudent to do the risk assessment of the individual for breast cancer before prescribing MHT.

There is no validated breast screening tool in India. Modified Gail model (Breast Cancer Risk Assessment Tool [BCRAT]) is a risk prediction tool that gives individual risk estimates for breast cancer development. BCRAT does not accurately predict the risk of breast cancer in Indian females. Few Indian hospital-based studies have shown a low sensitivity with the BCRAT.^[10] It is not surprising since the peak incidence of breast cancer is almost 10 years earlier. Moreover, breast cancer is a multifactorial disease with marked geographical, ethnic variation, genetic, reproductive, and lifestyle factors. There is a need for understanding the significant risk factors for breast cancer in the Indian population, which are different from the western population. The early age at menopause (below 12 years) was not a significant risk factor in some Indian studies. From the epidemiological data, an increase in age-standardized incidence rate is consistent with changes in some risk factors over time in India, such as later age at first birth, lower parity, lactation, increase in overweight and obesity, change in dietary and lifestyle pattern, and physical inactivity.

Researchers found that higher body fat levels in postmenopausal women with normal weight measured by dual-energy X-ray absorptiometry were associated

with an increased risk of invasive breast cancer at a median follow-up of 16 years.^[10] The most important modifiable risk factor for postmenopausal breast cancer is weight gain during adult life. Even a modest reduction of 2 kg is associated with lower breast cancer risk for women aged 50 years and older.^[11] Public health messages highlighting the importance of minimizing weight gain and healthy lifestyle choices such as limiting alcohol intake are essential for the prevention of breast cancer. In the absence of universal screening by mammography, modalities such as breast awareness, breast self-examination, and clinical breast examination play a role in downgrading the disease and improve survival rates.

How to decrease the risk of breast cancer in women using MHT?

Selecting women with lower risk: Before prescribing an MHT, it is prudent to evaluate breast cancer risk.

Education on lifestyle: Physical exercise and losing weight are factors associated with lower risk.

Treatment with lower risk MHT: Micronized progesterone or dydrogesterone is associated with a lower risk. Sequential therapy seems more favorable for the breast.

Like all medicines, MHT needs to be used appropriately, judiciously, and reviewed regularly.

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Conflicts of interest

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