Narrative Review

Postmenopausal Hormone Therapy and Its Association with Breast Cancer

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Abstract

With the cessation of estrogen and progesterone at menopause, the hormone withdrawal affects various systems in the woman's body. In earlier days, menopausal hormone therapy (HT) was prescribed for primary prevention of coronary artery disease (CAD) and osteoporosis, which were thought to be because of estrogen deprivation and epidemiologic data supported a beneficial effect of estrogen on the heart and bone. Later on, robust data from the Women's Health Initiative study comparing two HT trials demonstrated adverse outcomes in terms of excess risk of CAD, stroke, venous thromboembolism, and breast cancer. Even with risk stratification based on family history, approximately only 15% of women diagnosed with breast cancer have such a risk factor. This implies that family history will not be elicited in more than 85% of women who develop breast cancer. Literature review suggests that the prior use of conjugated equine estrogen (CEE) alone has the potential to be effective as an intervention, leading to a reduction in mortality due to breast cancer. Therefore, it is time to reevaluate the risk reduction strategies for breast cancer that are currently in practice. In terms of absolute numbers, for every 10,000 person-years of prior use of CEE alone, there would be only two fewer deaths from breast cancer and two fewer deaths secondary to its sequelae. This translates into a significant number of women in our country with a population of 1.38 billion (of which 48%, nearly 650 million, are women).

Keywords: *Breast cancer, hormone therapy, menopause*

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Introduction

Menopause is the permanent cessation of ovarian function, usually around 51 years of age (45–55 years in 95%). Withdrawal of estrogen and progesterone affects various systems in the woman's body. In earlier days, menopausal hormone therapy (MHT) was given as a preventive measure for coronary artery disease (CAD) and osteoporosis which were thought to be because of estrogen deprivation and literature supported exogenous estrogen to be of benefit. Later on, evidence from the Women's Health Initiative (WHI) study comparing two trials of hormone therapy (HT) (estrogen alone, combined estrogen-progesterone vs. placebo) comprising postmenopausal women at 63 years of mean age demonstrated adverse outcomes in terms of excess risk of CAD, stroke, and venous thromboembolism (VTE).[1] The association between breast cancer and HT remains debatable despite the availability of vast literature on this aspect. Therefore, there is a need to review the benefits versus risk of MHT with respect to breast cancer.

A woman has around 12% probability of being diagnosed with invasive breast cancer in her lifetime. It is said to be one of the most common malignancy, preceded by cancers of skin. When considering mortality from breast cancer, it is exceeded only by death due to lung cancer

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in women, about 1 in 36 chance of mortality because of breast cancer.[2] This risk becomes nearly 2-fold, with one first-degree affected relative and increases nearly 3-fold when two first-degree relatives have been diagnosed with breast cancer. Even though rare, the risk is there even if there is a history of a male member being affected with breast cancer, but its incidence is not reported in literature. Even with this risk stratification based on family history, approximately only 15% of women diagnosed with breast cancer have such a risk factor. This implies that family history will not be elicited in more than 85% of women who develop breast cancer.[3] For the familial cancers, the risk can be attributed to inherited DNA mutations of tumor suppressor genes such as (BRCA1 and BRCA2), which do not suppress abnormal cell growth, leading to cancer, and therefore result in breast cancer.[4]

Globally, the incidence of breast cancer is lowest in Asia, while the maximum number of cases is reported from Western Europe and North America.[5] Annually, more than 1 million new cases are added all over the world.[6] In women, breast cancer accounts for 23% of all malignancies. In India, it is the second most common cancer. A maximum increase in new cases is reported in urban areas with the highest incidence in Mumbai. According to estimates from the cancer registry data, nearly 800,000 new cases will be added annually. A review of previous years' data showed 50% increase in the incidence of breast cancer over the two decades (1965–1985).[7] The estrogenic and progestogenic activity of the female sex hormones, either endogenous or exogenous as oral contraceptives/menopausal HT, late age of childbearing, nulliparous, sedentary lifestyle, late menopause, and family history of breast cancer are the known risk factors. As there is an increase in incidence, especially from developed countries in older women >50 years of age, the contributing risk factors could be changes in reproductive patterns such as late age of pregnancy and assisted reproductive technologies, thus indicating prolonged exposure to sex hormones, early diagnosis of breast cancer with screening mammography, and unhealthy lifestyle patterns secondary to affluence.

The estimation of the association between menopausal HT and breast cancer such as type of and duration HT, age at start, and years since used, needs to be studied in similar settings. It is important to exclude confounding factors or bias, which can affect the outcome of the studies.

Various Factors that Need to be Studied Are

Estrogen

Estrogen is an important risk factor contributing to the risk of breast cancer. There are two possible postulated mechanisms for this; estrogen as a "mitogen" causes an increase in mitosis in breast tissue, which might lead to errors secondary to mutation, resulting in cancers. Furthermore, some genotoxins, which are estrogen metabolites, cause DNA damage directly and thus also act as carcinogens.[8] Exposure to naturally occurring environmental estrogen such as substances such as phytoestrogens termed "xenoestrogens" in plants/synthetic chemicals can mimic the effect of human estrogen produced from the ovary. Similar chemical structure of these two helps xenoestrogens occupy estrogen receptor in the body. In addition, estrogens may lead to the activation of other hormones such as relaxin (RLX), thereby indirectly stimulating mitosis. It is a well-known fact that RLX strongly influences growth and differentiation cells responsible for breast cancer (MCF-7).[9] As is seen in myometrial cells, estrogen has a stimulatory effect on RLX probably by inducing RLX receptors. Therefore, the role of estrogen may be implicated in breast cancer risk as it stimulates mitosis and acts during growth and development of breast and also indirectly stimulates cell division in breast through action on hormones such as RLX, leading to accelerated growth of estrogen-responsive tumors. This mechanism supports the association between endogenous hormone levels and breast cancer in postmenopausal women.[10]

Exogenous hormones as contraceptive (OC) pills in the reproductive age group are associated with slightly higher risk of breast cancer than women who had never used hormonal contraceptives. According to the duration of use, more than 10-year use had a slightly higher risk than for <1-year use. Overall, the increase was about one new breast cancer case per 7690 women who used hormonal contraceptives for a year. For younger women, <35 years of age who used hormonal contraceptives for a year had one additional breast cancer case for every 50,000 women.[11] The constituents of contraceptive pills contributing to the risk, whether estrogen or progesterone alone or in combination was not specified in the studies. It is a well-documented observation that this risk is directly proportional to the duration of hormones, as OC pills or as MHT.[12]

Knowing this, we need to understand the attributable risk posed by different drug combinations, duration of exposure, and risk due to prior use of HT from the evidence available from literature.

Exogenous Estrogen Exposure

The impact of exogenous estrogen, alone or as a combination with progesterone and its association with breast cancer, needs evaluation. It is well known that the

effect of endogenous estrogen in higher concentration and for the prolonged duration is a risk factor for breast cancer as seen in women with early menarche, late age of first pregnancy, nulliparity, no breastfeeding, and late menopause. Apart from these reproductive factors, increased bone mineral density (BMD) and high body mass index (BMI) are other risk factors. While the increase in BMD reflects prolonged exposure to endogenous and exogenous estrogen, a higher BMI and its association with postmenopausal breast cancer risk is because of higher estrogen levels in these obese women secondary to higher peripheral conversion of estrogen precursors to estrogen in adipose tissue. All these risk factors are depictive of high levels of endogenous estrogen which modify the risk of breast cancer proportionately in both post- and premenopausal women, especially the hormone receptor-positive cancers.

It is well known that estrogen is synthesized in adipose tissue and has a positive correlation with postmenopausal breast cancer. Indirectly, obesity is also associated with hyperinsulinemia, and insulin is a known mitogen. However, associations of breast cancer with high levels of insulin and/or insulin-like growth factor-I, independent of estrogen level are yet to be studied.[13]

There are conflicting reports from various studies regarding risk of breast cancer and exposure to exogenous estrogens. There was no increased risk as reported in the WHI trial. On the other hand, from the Nurses' Health Study of 28,835 women, an updated report shows that, in hysterectomized women, increase in breast cancer risk with long-term exposure to unopposed estrogen was statistically significant (RR for current use >20 years = 1.42).[14] The prospective cohort Million Women Study (MWS)[15] also reported similar outcome. Their observation differed from WHI and many other studies in the context that the MWS reported an increased risk even with <5-year HT. An important issue is regarding different types of estrogens used in different studies, which may have different risk stratification.

Type and Duration of Menopausal Hormone Therapy

The preparations containing both estrogen and progesterone are documented to be associated with greater risks than with estrogen alone. The long-term effect of prior use is not well documented in studies. As per the results of the comparison of conjugated equine estrogen (CEE) with placebo for the main clinical outcomes, the WHI randomized trial is the most referred trial about MHT, there was an increased risk of stroke, while the risk of hip fracture was less with the use of CEE, adverse cardiac events were not increased when studied over nearly 6.8 years before the trial was stopped, but there was a slight decrease in breast cancer risk in this arm of trial.[16]

On the other hand, the use of estrogen plus progesterone (E + P) as postmenopausal MHT at 5.6-year follow-up period was associated with an increased risk of breast cancer that too detected at a more advanced stage when compared with placebo.[17] Following these observations, the Food and Drug Administration made a change regarding their recommendation of HT that it should give at the lowest possible dose and for the shortest possible duration for therapeutic use when indicated. The new recommendation saw a decline in prescriptions of HT. However, this resulted in a high prevalence of vasomotor symptoms with no effective alternative therapeutic options in menopausal women, as estrogen is an effective recommended treatment. Hence, the decision of HT for subgroups of menopausal women with symptoms of estrogen withdrawal entails further evaluation of the therapeutic use of HT in terms of associated risks as well as their benefits.[18]

Post-WHI trial, many studies were conducted to confirm or refute the outcomes of this trial. A meta-analysis of 22 published reports regarding HT and these adverse effects also confirmed the findings of WHI. The authors conducted a systematic review of 22 studies involving 43,637 women to assess the outcome of long-term HT (minimum 1-year use) on various parameters related to cardiac health, malignancies, bone health, effect on nervous system, and mortality in women in perimenopausal transition and after menopause. The inclusion group consisted of postmenopausal American women, the majority were 60 years or older who had associated some other comorbid issues. Comparison of the results showed that the women who were prescribed combined HT for continuous use had more adverse cardiovascular outcome, increased risk of VTE, and stroke. Those taking estrogens alone had almost similar outcomes except the decrease in risk of breast cancer after 7 years of use[19] as was also reported in 2017 in an updated meta-analysis of 18 trials by the United States Preventive Services Task Force (USPSTF). Accordingly, the USPSTF recommended not to prescribe both combined estrogen-progesterone and unopposed estrogen (after hysterectomy) as a primary prevention for chronic medical disorders in women older than 60 years of age.[20] Shortcomings of this analysis were that the use of MHT for menopausal symptoms, as well as low absolute risks of MHT in younger menopausal women as shown in the WHI data were not discussed. In reality, women in the late fourth and an early fifth

decade in initial years of postmenopausal phase present with distressing symptoms because of estrogen withdrawal. For alleviation of menopausal symptoms, they need counseling regarding risks versus benefits for decision-making before staring MHT based on data from women of corresponding age group. For that, we need to have statistics based on evidence-based estimates of potential benefits and harms of HT with estrogen and progesterone for short-term use.

Type of Progesterone

Similar to estrogens, the type of progesterone may also affect the risk. In WHI trial, use of medroxy progesterone acetate (MPA), a synthetic progesterone, was associated with excess risk of breast cancer. In comparison, prescribing natural micronized progesterone in a prospective cohort study of approximately 80,000 women did not show this association.[21] The risk reduction was not significantly lower when compared between different types of other less used progesterone, use of estrogen, and micronized (natural) progesterone (RR 2·05) appeared to be somewhat lower for estrogen plus dydrogesterone. One such observation from WHI trial was increase in risk of invasive breast cancer with CEE and MPA (HT) in women on about 5.6 years of follow-up hazard ratio (HR) 1.24.[22] There was significant increase in RR during years 5–14 of progesterone-only MHT.[23]

Effect of Progesterone

It is usually hypothesized that progesterone may be responsible for an increase in mitotic activity in breast, thus leading to a greater number of errors in cell DNA that may eventually cause cancer.[24] The proliferative effect of progesterone on mammary tissue is further supported by the fact highest mitotic activity of the breast corresponds to the luteal phase of the menstrual cycle, which is a phase of increase in progesterone levels. Furthermore, mammographic breast density of women on combined estrogen-progesterone was more when compared to those on only estrogens, confirmed on breast biopsies showing more cell proliferation in the former.[25] This observation was confirmed in the randomized WHI study as well earlier epidemiologic studies.[26] Still, when compared for the effect of progesterone on proliferation of breast cells, results differ in *in vivo* and *in vitro* studies.[27]

Combination Therapy

Breast cancer in this group most likely to take HT for menopausal symptom is very low. In the Endocrine Society Clinical Practice Guideline, in terms of absolute numbers, the risk was three additional cases per 1000 women for 5 years of combined use conjugated estrogen-MPA.[28] On better side, using WHI data, the Endocrine Society Clinical Practice Guideline extrapolated that MHT with unopposed conjugated estrogen alone for 5 years in women in their 50s, there would be 2.5 less number of cases for every 1000 women users. When used for longer duration, during years 5–14 of estrogen-progesterone combination, the RR was 2·30 for continuous estrogen and progesterone, which was higher than for estrogen plus sequential progesterone, i.e., 10–14 days in a month (relative risk [RR] 1·93), $P < 0·0001$.[23]

Timing of Hormone Therapy

It is still not clear regarding the correlation between age of menopause and benefits and risks of MHT with age of initiation of MHT. When given early in menopause, MHT has a beneficial role in protection against cardiovascular disease than those who start late. On the contrary, the data on breast cancer and time of initiation MHT are limited, which indicates that risk of developing malignancy of breast in women starting MHT around the time of menopause may be greater than those who start it in later years of menopause.[21,29] The fact that those women who start MHT early also take it for longer durations which may be the actual risk factor rather than the time of initiation and needs to be considered when calculating the associated risk. This has been shown in literature that the risk of breast cancer appears to be increased in women on estrogen-progesterone therapy for longer than 4 or 5 years of use but not so with a lesser duration of use. These epidemiologic studies in their analysis showed that women who had a history of prior use of hormones for 5 years or more and were now current users of HT, the RR of developing cancer of breast was 1.35 when compared with never users.[12] The WHI study reported the increase in risk after only 3 years in women with a history of prior use of menopausal hormones.[17]

In a cohort of women aged 30–39 years who had initiated MHT, the significant increase in risks was seen among those who were still using either estrogen-progesterone combination or estrogen alone even after 15 years of starting, but number of participants in this group was less. On the other hand, in the later age group users (40–60 years), substantial number of women had started MHT, and the RRs were similar in all cohorts. Again, only few women who had initiated MHT beyond 60 years of age (60–69 years–135 cases), the risk of breast cancer was more for estrogen-progesterone versus estrogen-alone with current use during follow-up years 5–14 (RR 1·75 vs. 1·08).[23]

Prospective follow-up of women on MHT who were diagnosed with breast cancer showed that 50 years was

the mean age of menopause and of first use of MHT, had used MHT for mean of 10 years for current users, and 7 years for the past users. Among posthysterectomy 37,951 women, there were comparatively lesser (2710 or 7%) women on estrogen + progesterone, and majority (31 187 or 84%) were estrogen-only users. The risks were greater for estrogen-progesterone combined use, more so if taken daily rather than sequentially. The correlation with estrogen-receptor-positive tumors was higher as compared to receptor-negative tumors. There is little risk of breast cancer with vaginal estrogen in the recommended dose as there are decreased systemic levels of estrogens with topical vaginal preparations. The low-dose estradiol preparations either as 7.5 μg vaginal ring or 10 μg tablet resulted in plasma estradiol levels of ≤20 pg/ml even with prolonged use. The systemic estradiol levels ≥20 pg/ml were seen with 25 μg estradiol or 0.3 mg CEE.[23]

Prior Use of Menopausal Hormone Therapy

Prior use of hormones increases the risk of breast cancer significantly in women on combined E and P in comparison to those with no prior exposure even when other variables for risk stratification are eliminated, nearly twice in prior users.[17] Similar results were seen in WHI trial, in women on CEE + MPA versus placebo. This increase was initially observed in the 3rd year of use in those women with the prior use of menopausal hormones but was seen in 4th year of use in women with no such prior exposure.[21]

The main difficulty in such studies relates to differentiate the influence of HT on the risk of breast cancer from that due to the risk of breast cancer otherwise in that population. Other important factors to be considered are the years of use and age of menopause when the HT was initiated.[18] In this subgroup also women without prior use of HT, did not show any increase in breast cancer, but the emphasis should be on the need of continued follow-up as the risk increases with prolonged use of MHT. The interpretation of these outcomes when compared to WHI trial is that a longer duration of E + P use as HT than in WHI trial correlates with more risk. It is also postulated that the use of E and *P* as a combination increases breast cancer risk while posing difficulties in diagnosis, and that a safe interval regarding risk of breast cancer cannot be defined with certainty.[17,18] The update on long-term follow-up on the two trials in the WHI study revealed that, while the risks as well as benefits associated with administration of CEE + MPA disappeared overtime after their use was stopped with the exception of higher adverse cardiovascular events and a higher HR of breast cancer cases. Comparing with the estrogen only arm in women who had their uterus removed already for some indication, the benefits of CEE during the intervention phase showed a slight decrease in breast cancer, which continued in postintervention follow-up period also. Thus, CEE fared better in terms of both breast cancer and adverse CVD event than CEE + MPA.[30] Data about breast cancer risk associated with prior use more than 15 years before is scanty.[23] To assess such risk in past users, the higher duration-dependent risks after stopping MHT use persisted for more than a decade.

If there is direct correlation between the HT and breast cancer, it can be postulated that, in developed world, nearly 1 million cases of breast malignancy out of 20 million since 1990 may be due to HT. This risk is more in combined continuous versus E + sequential progesterone versus estrogen-only HT (from 6.3% to 8.3%/7.7%/6.8%, respectively). For lean women, estrogen-only HT had comparatively higher RR (1.5) than obese (1.1) in never user versus current users when studied in the 5–14 years of use in women with same BMI.[23]

Indian Scenario

As awareness for breast cancer risk factors has increased, so has the incidence. In India, it is most common cancer in the urban population, while where it is preceded by cancer of the uterine cervix in rural areas.[31]

The Indian Council of Medical Research in a survey reported that the incidence of breast cancer has almost doubled in metropolitan cities during 1982–2005. Globally, India along with the USA and China is the contributors of nearly one-third of total burden of the disease according to Globocan (a trusted source of global cancer statistics) 2012 is contributed by India along with the United States and China. The challenging situation in India depicts increase in incidence by 11.54% and 13.82% increase in deaths during 2008–2012 time period. Association of other variables such as breastfeeding, geographical area, and BMI with breast cancer has also been shown in a study in women from north India.[32]

Other risk factors include sedentary lifestyle, obesity, cigarette smoking, alcohol intake, exogenous hormone intake as oral contraceptive or hormone replacement therapy, and exposure to radiation for various indications.[33] The Breast Cancer Risk Assessment Tool, the "Gail model," uses a woman's own personal medical history for classifying the risk.[34] Known risk factors[33] enumerated above are not included in this tool probably because the evidence regarding their

association is not conclusive or their exact contribution to the risk cannot be determined accurately, or the accuracy of the tool decreases appreciably by taking these factors into account. Although there are significant therapeutic advancements, the development of methods for screening and early detection of the disease still needs more efforts. Postmenopausal women were more predisposed than premenopausal cohort for developing breast cancer. Estrogens may be the cause of increased risk in postmenopausal women with high BMI among never users compared to current users.[23] Lean women on estrogens may be at an increased risk compared to obese postmenopause, while past users and in premenopausal women breast cancer risk is more in obese compared to lean women.[23]

Some other mechanisms by which hormones/cytokines may also mediate the effects of estrogen, as well as obesity might affect cancer risk as a whole.[5]

Considering the use of HT and its risk stratification, the breast cancer screening program for women aged 50–69 years was initiated in Norway from 1996 to 2004. The incidence of breast cancer increased throughout the 190s and reached a plateau in 2002–2003.[35] Since then it has declined in this age group but not in younger women. These changes in incidence can be hypothesized secondary to two events: implementation of the Norwegian Breast Cancer Screening Programme and second the rise and fall in prescribing menopausal HT. Initially, there was a rapid increase in MHT use during the 1990s, which peaked in mid-2001. This was followed by fall in MHT use in 50% between 2002 and 2007. Bakken *et al*. analyzed data from the Norwegian women and cancer study to see whether this rise in incidence 1990s could be extrapolated either to use of hormones or to screening mammography. They reported that the current use of HT doubled the risk irrespective of the screening mammography when compared with never users. This could be the possible explanation for the rise in the incidence of breast cancer in Norway during that period. In countries where MHT is not much in use by postmenopausal women such as the Netherlands, changes in prescriptions of MHT did not translate into changes in the incidence of breast cancer. On the other hand, it was observed in many developed countries; there was a decrease in the incidence of breast cancer in women older than 50 years proportionate to decrease in use of HT. These trends further corroborate the already documented literature results of decline in risk with passage of time one HT is stopped.[36]

Exogenous estrogen and estrogen-progesterone as postmenopausal HT are categorized as group one carcinogens for human use as per the International Agency for Research on Cancer (American Cancer Society). As seen in WHI study, the combined use of estrogen (CEE) and MPA led to an increase in the incidence of breast cancer, while estrogen alone was associated with a decrease in risk. Therefore, to corroborate these observations mitigating progesterone, it was seen in experimental studies that some progestrones, including MPA, might hamper with estrogen-induced cell apoptosis. Another study indicates WNT4 and RANKL secretion triggered by progesterone may increase the migratory potential of breast cells. Still it cannot be the only factor as many cell divisions are needed even to result in a tumor of insignificant size of even 1 cm. Therefore, it is highly unlikely to state that HT is a very significant sole predisposing factor for breast cancer development. This was further reinforced by the results of WHI trial that most likely 96% of tumors existed when the participants were recruited. The mortality rates also were not higher in these women even after 18 years of follow-up of MHT.[37]

Another study[38] concluded that the incidence of invasive breast cancer with a favorable histological variety is higher in women on postmenopausal MHT, but the association is unclear regarding ductal carcinoma *in situ* or lobular and invasive cancer. This implies that the benefit versus risk association between postmenopausal HT and good prognosis breast cancer needs to be reassessed in that particular population. Assuming that like any other malignancy, women are at risk of breast cancer as they become older. Any other factor, which increases this probability, is an added risk for the women, and MHT is one such known risk factor.

Two independent randomized trials were initiated to determine the outcome of the use of menopausal HT in breast cancer survivors (BCS) – Hormonal Replacement Therapy after Breast Cancer – Is It Safe? (HABITS) trial and the Stockholm randomized trial. The outcome measures studied were in terms of recurrence-free survival, local or distant recurrence, mortality attributed to hormone use, and development of any new cancers. Because of slow recruitment and similar inclusion criteria, the two trials were analyzed together for safety and final outcome. It was reported in the combined analysis that menopausal HT had a significant role in the development of recurrence when prescribed to BCS.

The steering committee of the HABITS trial analyzed the available data separately, which indicated more than the acceptable risk of MHT in BCS; hence, the trial was terminated prematurely because of the increased recurrence risk at a median of 2.1-year follow-up (relative hazard 3.3). While in the Stockholm trial, the said risk was not increased even at a median follow-up of

4.1 years (Relative Hazard (RH) = 0.82). The main difference in the Stockholm protocol was lesser use of progesterone along with estrogen, which was not so in the HABITS trial. Furthermore, more women (52%) received adjuvant tamoxifen in the Stockholm trial than in the HABITS trial (21%), which may have further led to the decreased recurrence risk in Stockholm trial.

Thus, even though the results of these two well-designed trials differed significantly regarding the safety profile of HT in Breast Cancer Survivors (BCS), it can be speculated that prescribing estrogens with the addition of a minimal dose of progesterone for the management of menopausal symptoms may be safe in these groups of women. Still managing such women to provide a good quality of life as far as symptoms of hormone withdrawal after menopause is concerned poses a great dilemma for the treating physician.[39,40]

Although the WHI trial was terminated prematurely in 2004, still around 5% women continued the personal, nonprotocol use of hormones in the following 1 year, which further decreased to <4% over two extended periods of use between 2005–2010 and 2011–2012, respectively, and the data for these periods of use were collected annually. The authors analyzed the data till December 2017. for both trials (E and E + P). The primary objectives were the reduction in adverse cardiac events in the form of CAD as a measure of benefit. The increase in invasive breast cancer incidence was studied as a measure of risk. Mortality secondary to breast cancer, either directly because of it or indirectly because of its consequences, was also studied in long-term follow-up for all participants. The cumulative follow-up in the two trials showed higher annual incidence in terms of incidence of breast cancer (0.30% in CEE arm vs. 0.45% in CEE + MPA arm) as well as mortality in the CEE + MPA versus placebo trial when compared with CEE alone versus placebo within the same trial. Furthermore, breast cancers more commonly diagnosed at the higher stage with the use of CEE + MPA.

The authors also concluded from the long-term follow-up of these participants that prior use of CEE as HT versus placebo resulted in a lower incidence of breast cancer and mortality due to it. This benefit continued for more than 10 years after cessation of its use. The same results were not reported in CEE + MPA trial versus placebo as the incidence of breast cancer was higher in this arm and remained so even after a decade after discontinuation of the drug.[41]

Conclusion

In the absence of major specific contraindications, in women who have intolerable menopausal symptoms, one needs to weigh the benefits versus risk from short-term use of HT prescribed at a low dose. It may be prudent not to prescribe hormones for women with comorbidities such as at risk of CAD, thromboembolic disease, or those predisposed to malignancies (such as breast cancer/BCS, in women with an intact uterus). In the long-term follow-up study of two randomized trials in the WHI study, compared with placebo, among women who had a previous hysterectomy, prior use of CEE alone was associated with significantly lower breast cancer incidence mortality thereof. On the other hand, among women who had an intact uterus, prior randomized use of CEE plus MPA versus placebo was although associated with a significantly higher breast cancer incidence but difference in breast cancer mortality because of HT was not much significant.

Another gray area concerns the clinical benefit of various pharmacologic interventions (tamoxifen, raloxifene, and aromatase inhibitors), which lead to a reduction in the incidence of breast cancer, but the benefit is not translated in terms of decrease in mortality rates thereof. Hence, based on the results from the long-term follow-up of effects of HT on breast cancer in the WHI trial, it can be stated that the the prior use of CEE alone has a potential to be effective as an intervention, leading to a reduction in mortality due to breast cancer. Therefore, it is time to reevaluate the risk reduction strategies for breast cancer that are currently in practice. In terms of absolute numbers, for every 10,000 person-years of prior use of CEE alone, there would be only two fewer deaths from breast cancer and two fewer deaths secondary to its sequelae. However, the good news is that this translates into a significant number of women in our country with a population of 1.38 billion (of which 48%, nearly 650 million are women).

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Conflicts of interest

There are no conflicts of interest.

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