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Review Article

Menopausal hormone-replacement therapy and breast cancer risk: An updated and simplified view

Gargi Mukherjee[1], Vaishnavi Natarajan[2], Anindita Chakrabarty[1]

[1]Department of Life Sciences, Shiv Nadar University, Greater Noida, Uttar Pradesh, [2]Department of Biotechnology, Anna University, Chennai, India.

***Corresponding author:**
Anindita Chakrabarty,
Department of Life Sciences,
Shiv Nadar University, Greater
Noida, Uttar Pradesh, India.

anindita.ac@gmail.com

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ABSTRACT

Menopause, the menstrual cessation due to accelerated decline in ovarian function along with changes in the hormonal milieu, marks the end of reproductive fertility in women. This phenomenon is accompanied by various physiological and psychological symptoms, generally managed, and/or alleviated by menopausal hormone therapy (MHT). An association between MHT and the risk of developing breast cancer (BC), although controversial, is known for quite some time, particularly among combined MHT users. The risk varies with the time and type of MHT usage and persists after decades of treatment. The purpose of this review is to present an updated version of MHT and its association with postmenopausal BC risk.

Keywords: Breast cancer, Menopausal hormone therapy, Estrogen, Progesterone, Menopause

INTRODUCTION

Menopause is a natural phenomenon wherein the menstrual cycle ceases at around 50 years in Western countries and 46 years in India,[1-4] in response to the depletion of ova and fluctuation in hormone levels, i.e., lowered production of the E_2 and P_4, and elevated levels of pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) hormones.[5-7] Such fluctuating hormonal milieu is responsible for various adverse symptoms and associated disorders that curtail the quality of life in menopausal women.[6]

Menopausal hormone therapy (MHT), introduced in the 1960s, was extremely effective in managing menopausal symptoms. In the 1970s, a link between E_2 therapy and increased incidence of endometrial cancer in women with an intact uterus was found and resolved with combination MHT, i.e., a combination of E_2 and progestogen (generic term for progesterone and progestin). In the 1980s, the federal drug administration, USA approved MHT usage for managing menopausal symptoms and associated conditions.[8]

MHT usage declined dramatically when the Women's Health Initiative (WHI) published its findings in 2002, reporting excess risk of breast cancer (BC) with MHT, particularly in the combination regimen. A re-evaluation of the WHI trial data failed to find any statistical significance in the relative risk (RR) after adjusting for confounding factors.[9] Ultimately, findings contradicting the WHI trials were published.[10-12] Recent cohort studies, case-control studies, and meta-analyses have re-established the link between combined MHT usage and BC risk and also highlighted the risk associated with the type and timing of MHT usage.[13-15] The relationship between MHT and BC risk in menopausal women reviewed herein is preceded by a brief discussion on menopause

and its symptoms. We intend to convey this important topic to non-expert readers, especially the students.

THE MENSTRUAL CYCLE, MENOPAUSE, AND ITS ORIGIN

A normal menstrual cycle repeats every 28 days, beginning with the onset of menstrual discharge and terminating at the start of the next menses. It comprises three phases: Follicular (pre-ovulatory), ovulatory (release of oocyte), and luteal (post-ovulatory), driven by E_2, P_4, FSH, and LH.[1,2]

The follicular phase is marked by the start of menstrual bleeding wherein, there is an overall decline of E_2 and P_4 levels and a slight increase in the pituitary FSH, stimulating the development of several ovarian follicles. Further, in the follicular phase, the dominant follicle matures and accumulates E_2-producing granulosa cells; rising E_2 level suppresses pituitary gonadotropin-releasing hormone secretion, lowering FSH.[16,17]

The end of the follicular phase and initiation of the ovulatory phase are marked by surges of LH and FSH. The surge of FSH coinciding with the LH surge is lesser and function-wise not well understood.[17]

In the luteal phase, in absence of fertilization, there is a decline in the level of LH and FSH levels, the ruptured follicle closes and forms corpus luteum, producing P_4.[17]

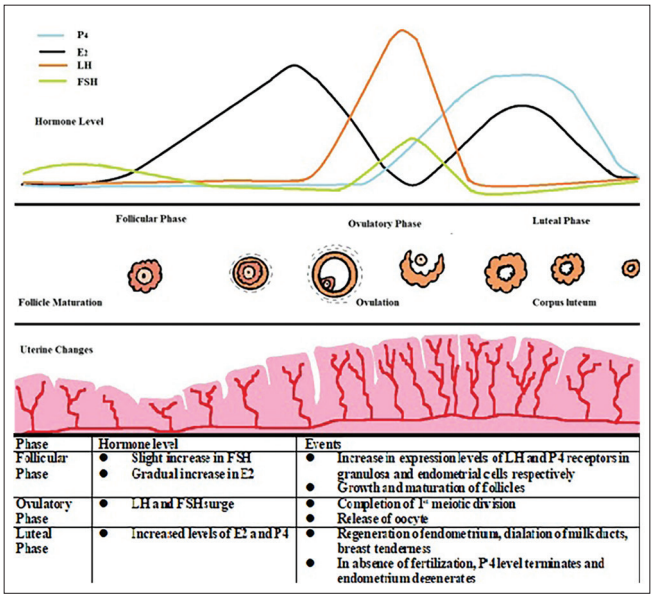
Absence of fertilization results in the degeneration of the corpus luteum and termination of P_4 secretion. With the decline in E_2 level, endometrial breakdown, shedding and menstrual bleeding commence. During the late luteal phase, follicles for the next ovarian cycle are recruited, they resume growth and start secreting E_2, assisting the regeneration of the endometrial wall.[2]

Figure 1 represents hormonal profile, ovarian and uterine changes, and important events of the menstrual cycle.[17]

By definition, menopause is an irreversible cessation of menstruation due to depletion of the follicular function of oocytes, indicating the end of natural female reproductive life. Stages of Reproductive Aging Workshop classifies ten reproductive stages. Five stages (−5−−1) before the FMP: final menstrual period, that is, Stage 0 followed by two more stages (+1−+2). −5−−3 is classified as the reproductive phase, followed by menopause transition, (−2−−1) characterized by amenorrhea, increased anovulatory cycles, variable cycle lengths, irregular FSH concentrations, and +1 and +2 as post-menopause.[5] Although the size and number of follicles shrink, not all follicles become unresponsive. However, due to high FSH concentration, folliculogenesis is dysregulated. The decrease in the follicular number and size beyond the threshold causes anovulatory cycles lacking folliculogenesis followed by FMP; amenorrhea for 12 months.[6]

According to the Indian Menopause Society, the different phases of menopause are natural menopause, premenopause, and perimenopause (indicative of the period exactly before and after 1 year of the final menopausal period (FMP).[4]

Many theories and hypotheses have been put forward explaining the origin of menopause. Some theories suggest menopause to have originated during the *Homo erectus* period and the rest suggest it as a recent phenomenon.[18] Broadly, these theories can be classified into two. One views it as an adaptive phenomenon or grandmother effect, according to which decreasing reproductive life span improves fitness.[19] The other views menopause as an antagonistic pleiotropic phenomenon.[19] According to the latter, during childbirth, ovarian hormones reach the highest level and drop within 24 h following parturition, generating a hypoestrogenic environment similar to menopause. Although both phenomena experience the same hormonal and epigenetic changes, these changes are beneficial during lactation and are detrimental during menopause. After childbirth, a low level of E_2 results in an elevation of serum lipoprotein concentration, which improves fat content in breast milk. In menopausal women, the same scenario increases the risk of cardiovascular diseases (CV), vascular inflammation, and arteriosclerosis. Dyslipidemia in menopausal women when combined with heightened serum inflammatory markers and hypertension affects mood and memory.[19] In 2010, around 3.7 million cases of dementia were reported in India, of which 2.1 million were women. It is expected that such cases would be double in 2030. It has been shown that the risk of depression increases 2.5 times more in menopausal women rather than in premenopausal.[4] After parturition, elemental



Phase	Hormone level	Events
Follicular Phase	• Slight increase in FSH • Gradual increase in E2	• Increase in expression levels of LH and P4 receptors in granulosa and endometrial cells respectively • Growth and maturation of follicles
Ovulatory Phase	• LH and FSH surge	• Completion of 1st meiotic division • Release of oocyte
Luteal Phase	• Increased levels of E2 and P4	• Regeneration of endometrium, dialation of milk ducts, breast tenderness • In absence of fertilization, P4 level terminates and endometrium degenerates

Figure 1: Hormonal profile, ovarian and uterine changes across menstrual cycle.[17]

calcium is displaced from the lumbar spine for the production of breast milk, which in menopausal women enhances the risk of osteoporosis.[19] According to the Indian Menopausal Society, osteoporosis occurs in Indian women 10–20 years earlier than in Caucasians.[4] Heat dissipation helps in heating the infant postpartum, which during menopause leads to hot flushes and other vasomotor discomforts.[19] There is yet another theory that explains menopause as a consequence of reduced fertility associated with the accumulation of deleterious mutations in older women due to mating preference for younger females.[19]

HORMONE REPLACEMENT THERAPY FOR MENOPAUSAL SYMPTOM MANAGEMENT

The psychological and physiological symptoms that accompany menopause, adversely affecting the quality of life, are listed in Table 1.[20,21]

A longitudinal study by Penn Ovarian Ageing observed that 75% of postmenopausal women experienced joint pain and 73% suffered hot flushes.[21] A multi-ethnic study assessed the bone mineral density and found it to decline rapidly during the transition and post-menopause phase; the rate being slower in African-American women compared to Asian women.[22] The Vaginal Health: Insights, Views, and Attitude studied a large cohort of women and observed that more than 70% of menopausal women experienced some kind of vaginal discomfort; 24% experienced pain during intercourse, 35% observed involuntary urination, 22% suffered soreness, 15% experienced itching, and 17% suffered burning sensation.[23]

During the normal reproductive cycle, E_2 levels fluctuate between 220 pmol/l and 918 pmol/l in the follicular phase and between 275 pmol/l and 1650 pmol/l in the luteal phase. During menopause, these fall below 41 pmol/l. Although MHT does not mirror an E_2 environment as that of the normal reproductive cycle, it produces enough for managing the climacteric symptoms.[24] MHT successfully alleviates the symptoms that terribly affect the quality of life and also prevents diseases associated with E_2 deprivation. MHT can be categorized as E_2-only therapy (ERT) or combined E_2 + P_4 therapy (EPT). Table 2 lists the most common E_2, and P_4 preparations of MHT.[24-26] ERT recommended for women without a uterus in formulations such as conjugated equine estrogen (CEE) and estradiol (E_2) is administered in many ways, orally, transdermally, intramuscularly, intranasally, subcutaneously, and locally. EPT, on the other hand, is prescribed for women with an intact uterus, either continuously or cyclically. This is because E_2 is mitogenic for endometrial cells and hence is combined with P_4.[24-26]

Below, we will briefly discuss some of the menopausal symptoms and associated diseases that are successfully managed by MHT.

Vasomotor symptoms (VMS)

Vasomotor discomforts such as hot flashes and sudden warmth sensation in the chest are common in postmenopausal women and are caused due to the narrowing of the thermoregulatory neutral zone in the hypothalamus as a response to the reduction in E_2 levels. ERT reduces hot flashes by 70%. However, discontinuation of MHT leads to a 50% chance of recurrence of VMS.[20, 24, 27]

Vulvovaginal atrophy and urogenital tract infection

Low E_2 levels during menopause cause an increase in vaginal pH, thereby leading to vulvovaginal atrophy.[25] Approximately 50% of postmenopausal women experience urogenital discomforts. Deprivation of ovarian hormones makes it susceptible to bleeding, pathogenic infection, bladder leakage, and painful urination. MHT alleviates such discomforts to a large extent.[28]

Cardiovascular diseases (CV)

The risk ratio (RR) for mortality due to CV was found to be 0.5 compared to overall mortality (RR = 0.7), with a 95% confidence interval (CI) in MHT users.[20] Data from recent studies such as early vs. late intervention trial with estradiol (ELITE) and the kronos early estrogen prevention study (KEEPS) indicate a low risk of CV in young symptomatic women but is not recommended as primary or secondary prevention of CV.[29]

Diabetes mellitus

In Indian women, after menopause chances of Type 2 diabetes, the occurrence is more prominent.[4] MHT successfully lowers such risk, but the trend is not maintained after discontinuation.[20] The American Association of Clinical Endocrinologists does not recommend MHT for diabetes prevention and makes

Table 1: Symptoms associated with menopause.[20,21]

S. No.	Metabolic symptoms	Organic symptoms	Somatic symptoms
1	Diabetes	Urogenital infections and inconsistency	Vasomotor symptoms
2	Cardiovascular diseases	Weight Gain	Vaginal discomforts
3	Osteoporosis	Increased breast density	Depression, mood swings
4	Atherosclerosis	Skin thinning, itchiness and irritability	Sleep disorder, dizziness and irritability

Table 2: Different estrogen and progesterone preparations for MHT.[24-26]

A. Estrogen-based preparations and doses			
Oral	1	17 β-Estradiol (17 E_2)	0.5 mg/d
	2	Ethinyl Estradiol	2.5 mcg/d
	3	Conjugated Estrogen (CE)	0.3–0.45 mg/d
Transdermal	1	17 E_2 patch	0.014–0.0375 mg/d
	2	17 E_2 gel	0.25 or 0.75 mg/d
	3	17 E_2 spray	1.53 mg/d
	4	17 E_2 emulsion	8.7 mg/d
Vaginal	1	17 E_2 vaginal cream	0.2 mg/d
	2	CE vaginal cream	0.3125 mg/d
	3	17 E_2 vaginal tablet	10 mcg/d
	4	17 E_2 vaginal ring	2 or 12.4 mg/ring
Injectable	1	CE	25 mg
	2	Estradiol Valerate	10 g/ml
B. Progesterone-based preparations and doses			
Oral	1	Medroxyprogoesterone Acetate (MPA)	1.5–2.5 mg/d
	2	Norethindrone Acetate (NETA)	0.1 mg/d
	3	Drospirenone (DRSP)	0.25 mg/d
	4	Micronized Progesterone	100–200 mg/d
Transdermal	1	NETA	0.14 mg/d
	2	Levonorgestril (LNG)	0.015 mg/d
Injectable	1	MPA	50 mg/ml
	2	Micronized Progesterone	50 g/ml
C. EPT preparation and their available strengths			
Oral	1	CE and MPA	0.625 mg CE and 2.5 mg MPA/d
Oral	2	17 E_2 and Norgestimate	1 mg 17 E_2 for 3d followed by 1 mg 17 E_2 and 0.09 mg Norgestimate for next 3d (cyclic)
Oral	3	17 E_2 and NETA	1 mg 17 E_2 and 0.5 mg NETA/d
Oral	4	17 E_2 and DRSP	0.5 mg 17 E_2 and 0.25 mg DRSP/d
Oral	5	Ethinyl Estradiol and NETA	5 μg Ethinyl Estradiol and 1 mg NETA/d
Transdermal	6	17 E_2 and LNG	45 μg 17 E_2 and 15 μg LNG/d
Transdermal	7	17 E_2 and NETA	0.05 mg 17 E_2 and 0.14 mg NETA/d

https://www.rxlist.com/prefest-drug.htm#description, https://www.uptodate.com/contents/treatment-of-menopausal-symptoms-with-hormone-therapy.
MHT: Menopausal hormone therapy

clear that all risk factors should be considered carefully before administering MHT to diabetic women.[15]

Due to E_2 deprivation, menopausal women experience a high risk of Type I osteoporosis and musculoskeletal discomforts,[20,30,31] sleeping disorders,[20,28] rapid mitochondrial dysfunction and elevated level of oxidative stress, leading to hypercholesterolaemia[32] hypertension,[33] liver disease,[34] and various other discomforts, which may be managed with MHT.[35,36] Table 3 lists some of the common advantages and disadvantages of MHT.[37]

ASSOCIATION BETWEEN HORMONE REPLACEMENT THERAPY AND BC RISK

BC is one of the most common cancers in women. Globally, around 1.5 million, approximately 25% of women are diagnosed with BC every year. In India, it is ranked number one cancer among females. There are several risk factors, such as aging, family history, mutations in genes encoding breast cancer 1 and 2 gene (BRCA1/2), ataxia talangiectasia and Rad3 related (ATM), tumor protein p53 (TP53), and phosphatase and tension homolog deleted on chromosome 10 (PTEN), and high levels of growth factor receptors and steroid hormones (HER2 and estrogen, respectively).[38] Another important risk factor for BC, especially in the postmenopausal setting, is metabolic syndrome (MetS), consisting of a combination of cardiovascular risk factors such as central obesity, hyperglycemia, hyperinsulinemia, hypertension, and hypertriglyceridemia. This is partly due to the association between insulin resistance and heightened estrogen/progesterone levels. Chronic oxidative stress and inflammation associated with MetS could also contribute to breast carcinogenesis.[39]

Continued MHT usage is connected to a greater risk of BC. In addition, ERT increases the risk of endometrial cancer; hence, it

Table 3: MHT advantages and disadvantages.[37]

S. No.	Advantages	Disadvantages
	A. Overall	
1	Relieves vasomotor symptoms	Increases risk of breast cancer
2	Improves sleep, helps overcome anxiety and irritability	Increases risk of endometrial cancer (ERT regime)
3	Helps overcome vaginal bleeding, improves libido, and decreases dyspareunia	Increases risk of ovarian cancer
4	Alleviates urinary tract discomfort	Increases risk of thrombosis
5	Inhibits bone resorption and prevents osteoporosis	Increases risk of vaginal bleeding
6	Prevents metabolic disorders such as diabetes and cardiovascular disease	Nausea, liver damage etc.
	B. On the basis of the estrogen component	
E_2 component	**Advantages**	**Disadvantages**
Oral E_2	Easy administration	Side effects at high doses, such as high cholesterol levels
Ethinyl E_2	Stable and low-dose application	Thrombosis, hypertension, platelet aggregation, and urinary secretion of calcium
CE	Potent	Release at high doses, results in high levels of renin in plasma
Transdermal	At low dose no variation in cholesterol levels and low insulin resistance	Expensive, variable absorption and adverse skin reaction

MHT: Menopausal hormone therapy

is only limited to women who have undergone a hysterectomy. Women with an intact uterus are prescribed combined EPT.

In a trial conducted by the Women's Health Initiative (WHI) in 2002, women with an intact uterus (n=8506) received a combined regimen of CEE and medroxyprogesterone acetate (MPA) and the hysterectomized settings (n = 5310) received CEE only. During the interventional phase, it was found that HR (hazard ratio) with 95% CI for BC was 1.24 in the combined regimen and 0.79 in the unopposed regimen. In the post-interventional phase, the HR for EPT was 1.32 and for ERT was 0.80. After a 13-year follow-up, the HR for EPT was 1.28 and that of ERT was 0.79, indicating a higher risk of BC in the combined regimen. Observation of a 26% increase in BC in women receiving EPT with a relative risk (RR) of 1.26 by WHI[40] led to widespread panic and the downfall of MHT usage.[11,41] However, in the WHI study, the RR was calculated from 30 cases/10,000 non-users versus 38/10,000 MHT users, representing a very minute absolute risk of 8/10,000 or 0.08% per year. Furthermore, the mean age of women in WHI was 63 years, but MHT is normally prescribed to symptomatic women below 60 years of age and around 70% of women in the study started MHT after entering the study. A re-evaluation of WHI results suggested that the risk is statistically insignificant after adjusting for confounding factors.[9,42] Santen *et al.* developed biological and computer-aided models and calculated the percentage of *de novo* and occult tumors in the WHI study. He also analyzed the effects of EPT for 5 years or less on BC risk. Only 6% of the tumors diagnosed over a 5–7 year period occurred *de novo*, leaving 94% of pre-existing tumors growing in size reaching the diagnostic limit. This study concluded that HR for EPT used in the WHI trial was due to the pro-proliferative ability of the combination hormones to enhance the growth of already existing tumors rather than initiating new tumors. It was also found in this study that natural P_4 rather than synthetic progestogens is a safer choice.[10,12]

Although the WHI study was criticized, recently several studies have confirmed a similar trend between MHT use and BC risk. It has also been found that prolonged exposure to either kind of MHT (ERT and EPT) results in a significant risk of developing BC. Kerlikowske *et al.* have observed a RR of 1.49 with 95% CI for BC risk in prolonged (more than 5 years) EPT users.[43] BC risk concerning the type of MHT in the E3N-EPIC cohort observed in around 900 cases of invasive breast carcinoma out of 54,500 postmenopausal women during follow-up has been RR of 1.1 for ERT and 1.3 for EPT. It has also indicated that micronized progestogens are safer than synthetic progestogens as the RR for EPT (synthetic) has been 1.4 and the RR for EPT (micronized) has been 0.9.[44] A meta-analysis of data from four randomized trials has reported 0.79 RR for ERT and 1.24 for EPT, indicating a higher risk of developing BC in EPT. This particular study has also suggested that the risk is higher in the present users than in past users.[45] Another France-based large case-control study (1555 menopausal women, 739 cases and 816 controls) has confirmed the risk of BC concerning the type of MHT administered. In this study, the odds ratio (OR) for long-term (>4 years) ERT present user is 1.01, and 1.55 for EPT, suggesting that EPT enhances BC risk. It has also compared

the OR for EPT with natural progestogen with the synthetic version and found a difference in values of 0.79 and 2.07, respectively. The study has further attempted to differentiate the OR of EPT with synthetic progestogen as progesterone-derived and testosterone-derived and reported these as 1.92 and 9.47, respectively. Finally, this study has revealed that continuous administration (OR = 2.7) of MHT poses a greater risk than cyclic regimen and the risk of developing ER+ and lobular tumor (OR=1.7 vs. 2.48) is high in EPT than in ERT.[46] Another meta-analysis pooled information from 58 studies has analyzed the type and timing of MHT and BC risk. Among 143,887 postmenopausal women diagnosed with invasive BC, 51% were users of MHT, implying an overall risk of BC in MHT users compared to non-users. In this study, RR for ERT has been found as 1.33, with no significant difference among different estrogen supplements (CEE and E_2), or route of application, although, vaginal estrogen seemed to be safer a choice. For EPT, RR has been 2.08, almost similar for all forms of progestogens including micronized progestogens except dydrogesterone (RR = 1.39). Continuous EPT (RR = 2.3) has been found to be more harmful than cyclic (RR = 1.93), with the probability of ER+ tumor (RR [ERT] = 1.45, RR [EPT] = 2.4) being higher than the ER- type (RR [ERT] = 1.25, RR [EPT] = 1.42). Furthermore, risk of developing lobular tumor (RR [ERT] = 1.5, RR [EPT] = 2.7) has been more than ductal tumor (RR [ERT] = 1.25, RR [EPT] = 1.8). This study has also found that lean MHT users (RR [ERT] = 1.5, RR [EPT] = 2.36) are at higher risk of developing BC than obese women (RR [ERT] = 1.1, RR [EPT] = 1.6), even though higher body mass index (BMI) increases the risk of BC.[13] A recent nested case-control study has observed an OR for long-term ERT to be 1.11 and 1.15 for CEE and E_2, respectively, and OR for long-term EPT to be 1.88, 1.79, 1.87, and 1.24 for norethisterone acetate, levonorgestral, medroxyprogesterone, and dydrogesterone, respectively. This study has reported a low risk associated with dydrogesterone, which further diminishes within 2 years of discontinuation, but this trend does not apply to other progestogens. It confirms a lower risk of BC with greater BMI and a linear increase in the chance of developing BC with a longer duration of use, as reported by other groups.[14] The risk of BC recurrence in MHT users is unclear. A randomized trial Hormone Replacement Therapy after BC – is it safe? with a mean follow-up of 4 years suggests that HR for BC recurrence is 2.5 (95% CI) whereas the Stockholm trial suggests otherwise (HR = 0.8, 95% CI).[47] Table 4 lists the studies reporting increased BC risk with MHT usage.

MOLECULAR AND GENETIC EFFECTS OF HORMONE REPLACEMENT THERAPY ON BREAST TISSUE

Progestogens administered during EPT such as MPA have been found to enhance the proliferation and metastasis of BC cells through genomic and non-genomic mechanisms. For example, it activates various signaling pathways such as mitogen-activated protein kinase or binds to steroid receptors, enters the nucleus, and activates or suppresses target gene expression, causing BC initiation or progression.[48,49] With menopause, the ovary stops producing E_2, unlike adipocytes. The aromatase enzyme catalyzes the conversion of androgens to E_1 and E_2, while the steroid sulfatase and estrogen sulfotransferase convert E_1S to E_1 and E_1 to E_1S, respectively. The 17-hydroxysteroid dehydrogenase enzyme is of two types, with Type I catalyzing the reduction of E_1S to E_2, whereas Type II catalyzing the reverse reaction.[50] It was found that progestogens stimulate mRNA levels of E_2-producing enzymes, elevating the BC risk.[48] Horwitz and Sartorius suggested that the progestogens component of EPT reactivated the stem cell population in BC.[51]

A Swedish study with 131 ER + BC samples observed alterations in 276 genes associated with MHT use, most of which were either involved in DNA repair or cell cycle regulation.[52] Another study observed that BC risk in combined MHT users rose high in those women having one rare allele of CYP1A1 and CYP1B1 polymorphisms. The enzymes encoded by these two CYP450 are involved in the synthesis of catechol estrogen and estrogen quinone forming DNA adducts and causing enhanced proliferation of BC cells.[53] A study based on data from the Normal Breast Study analyzed 54 MHT users (26 EPT and 12 ERT) and 36 non-MHT users. It identified 527 CpG sites (cytosine followed by guanine residues) located within 403 genes and 97 intergenic regions. It was found that DNA methylation was more prevalent in MHT users than non-users, which was further affected by factors such as duration and recentness of MHT usage. Strong modifications were observed in three CpG sites present on chromosomes 1, 2, and 3 in MHT users for non-

Table 4: Studies reporting positive association between BC risk and MHT usage.

S. No.	Study type	BC risk	References
1	American WHI trial	Yes	[40]
2	Screened population trial	Yes	[43]
3	E3N-EPIC: Etude Epide´miologique de femmes de la Mutuelle Ge´ne´rale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition French cohort trial	Yes	[44]
4	Meta-analysis	Yes	
5	France-based case control trial	Yes	[46]
6	Meta-analysis	Yes	[13]
7	Nested case-control trial	Yes	[14]
8	Hormone replacement therapy after breast cancer (HABITS) trial	Yes	[55]

MHT: Menopausal hormone therapy, BC: Breast cancer, WHI: Women's Health Initiative

Table 5: Molecular effectors of MHT contributing to BC risk.

S. No.	Molecules/processes/cell populations affected by MHT	Contributing to BC risk	References
1	MAPK and steroid hormone receptors	Yes	[48,49]
2	E_2 producing enzymes	Yes	[50]
3	Cancer stem cell population	Yes	[51]
4	CYP1A1and CYP1B1 polymorphism	Yes	[53]
5	DNA methylation	Yes	[54]

MAPK: Mitogen-activated protein kinase, MHT: Menopausal hormone therapy, BC: Breast cancer

users, two among these sites were hypermethylated and the other hypomethylated. Another CpG site (INPP4BCpG) was found to be highly methylated. Interestingly, loss of function of tumor suppressor gene INPP4B is predominant in many BC. These epigenetic modifications triggered by MHT might contribute to BC development and progression.[54] Table 5 summarizes the molecular effectors of MHT contributing to increased BC risk.

CONCLUSION

Although MHT alleviates the majority of menopausal symptoms and improves the quality of life, the risk of developing BC is highly significant with its usage. The risk is greater with EPT compared to ERT and non-users, and it persists even after a decade of discontinuation. Factors such as genetic susceptibility, BMI, lifestyle, medical history type of regimen, dosage, duration, and individual response to MHT influence the associated BC risk. Thus, all risk factors must be considered and an appropriate MHT treatment strategy should be employed.

Declaration of patient consent

Patient consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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