JMM Journal of Menopausal Medicine
pISSN: 2288-6478, eISSN: 2288-6761
https://doi.org/10.6118/jmm.21035
J Menopausal Med 2022;28:47-51
REVIEW ARTICLE

Hormone Therapy and Risk of Breast Cancer: Where Are We Now?

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Several studies have examined the clinical benefits of hormone replacement therapy (HRT). However, because long-term use of HRT has been implicated as a risk factor for the development of breast cancer, some women remain skeptical when considering this therapy to address their vasomotor symptoms. Hence, physicians and nurses should actively engage in constructive discourse with their patients regarding HRT while specifically reviewing the potential risks of its extended use as well as provide the available medical alternatives the patients could potentially use.

Key Words: Breast cancer, Estrogen, Hormone replacement therapy, Progestin

INTRODUCTION

Breast cancer is the most common female malignancy in the United States, afflicting 281,500 women in 2020 [1]. Fortunately, nearly two-thirds of breast cancer patient cases are diagnosed at a localized stage, wherein the 5-year survival rate is favorable. Age (45 to 75 years) is a primary risk factor for breast cancer development [2], in addition to ovarian hormones, the presence of BRCA1 (BReast CAncer gene 1) and BRCA2 (BReast CAncer gene 2) gene mutations, reproductive history, and previous chest irradiation [3,4].

HORMONE THERAPY AND BREAST CANCER

Since the 1970's, approximately 600 million women from western countries have used hormone replacement therapy (HRT) [5]. HRT, encompassing conjugated estrogens alone, or in combination with progestin, is indicated to attenuate vasomotor symptoms, forestall cognitive deficits, and avert cardiovascular disease [6,7]. However, several randomized clinical trials and observational studies have impugned the safety of HRT because of the medication's putative relationship with breast cancer incidence and mortality [5,8-10].

Estradiol heightens the risk of breast cancer in postmenopausal women and preclinical studies have demonstrated that progestin engenders progenitor cells in both human and breast cancer cells [11-13]. While estrogen and progesterone levels significantly decline following menopause, HRT-induced blood estrogen levels correlate with an increased incidence of estrogen receptor-positive breast cancer, especially in women with a higher body mass index [13]. Studies have remarked that perhaps, estrogen-alone is safe, whereas estrogen/progestin ostensibly accords a countervailing or detrimental effect [14,15]. Hence, when evaluating a woman's lifetime risk for developing breast cancer, one should consider the persistent inclusion of these two agents, either independently or collectively.

WOMEN'S HEALTH INITIATIVE (WHI) AND MILLION WOMEN TRIALS

The WHI initially reported on the controversial ben-

Received: December 21, 2021 **Revised:** June 2, 2022 **Accepted:** August 8, 2022
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efits and potential complications inherent in HRT in their 2002 landmark study [10]. The trial comprised 16,608 healthy postmenopausal women with a uterus who underwent treatment with conjugated equine estrogens (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) or placebo for a median duration of 7.2 years. The HRT group was associated with more breast cancer-related deaths compared to the place group (2.6 vs. 1.3 per 10,000 women annually), resulting in clinical trial termination. In 2004, the WHI evaluated 10,739 postmenopausal women with a prior hysterectomy, ages 50–79 years, who underwent either conjugated equine estrogens (0.625 mg/d) or placebo. This study was also prematurely closed due to the elevated risk of stroke in the HRT group although interestingly, the results suggested a possible decreased incidence in breast cancer [8].

In the Million Women Study, 1,084,110 women from the United Kingdom (U.K.), ages 50–64 years, reported their use of HRT (estrogen alone or progestin-estrogen) and were surveilled to ascertain the subjects' breast cancer incidence and mortality [9]. The results suggested that women who underwent estrogen-only or estrogen-progestogen had a 1.3-fold risk or 2-fold risk of developing breast cancer, respectively. Following the results from the WHI and U.K. trials, the use of HRT declined significantly [16]; and from 2001 to 2004, an 8.6% decrease in breast cancer incidence was reported for women, 50 years or older [17].

WHI FOLLOW-UP STUDIES

Manson et al. [18] reported on the updated findings from the two WHI studies, indicating that hormone therapy may be beneficial in terms of all-cause mortality, with fewer risks (e.g., coronary heart disease, stroke) among women 50 through 59 years. Moreover, the risks from conjugated equine estrogens plus medroxyprogesterone were primarily inherent to the intervention phase, and both the risks and benefits were ultimately ephemeral throughout the post-intervention period.

In 2017, the WHI clinical studies [15] reported that there were 7,489 deaths throughout the treatment and surveillance periods; all-cause mortality was 27.1% for the women who underwent HRT vs. 27.6% in the placebo group (i.e., neither estrogen-alone nor in combination with medroxyprogesterone acetate was associated with an increased risk of cancer mortality). Accordingly, the North American Menopause Society revised its guidelines [19]; HRT was recommended for women who were younger than 60 or within 10 years of menopause, especially if they were at higher risk for bone loss or fracture.

A prolonged review of the WHI trials in 2019 suggested that estrogen-alone had a countervailing effect on breast cancer incidence, compared to the increased risk of breast cancer from estrogen/progestin therapy [14]. There was a 23% reduction in breast cancer for the postmenopausal woman who received estrogen therapy-alone, whereas the risk of breast cancer and breast cancer-related death was elevated by 29% for the women treated with estrogen/progestin, an effect that transcended 10-years of discontinued use.

U.K. HRT STUDIES

Despite the findings from the 2019 WHI study, an epidemiological study conducted in the U.K. reported that of the 108,647 postmenopausal subjects who developed breast cancer, 51% had been treated with HRT [5]. Interestingly, the elevated risk encompassed all types of HRT (vaginal estrogens excepted), particularly combined estrogen/progestin. The increased risk from estrogen/progesterone was evident for patients on therapy for 1–4 years, with a two-fold risk during years 5–14, particularly in women who ultimately developed estrogen receptor-positive breast cancer.

When considering the specific risks according to age, women who used HRT for 5 years, commencing at age 50 years, exhibited a significant increase in risk for breast cancer at ages 50–69 years (half of the elevated risk was attributed during the first 5 years of current HRT use and the other half was ascribed to the subsequent 15 years of prior use) [5]; this represents an absolute increase of approximately 2% for women undergoing estrogen/progesterone. Additionally, the corresponding risks with 10 years of use starting at age 50 years would be nearly two-fold.

In a subsequently published U.K. nested-control study, the researchers compared the impact of HRT on 98,611 breast cancer patients, ages 50–79, to 457,498 female control subjects [20]. Overall, HRT use was associated with an increased risk of breast cancer (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.19 to 1.23). Intriguingly, the elevated risk was attributed to both estrogen and progesterone (OR, 1.26; 95% CI, 1.24 to 1.29) and estrogen-only therapy (OR, 1.06; 95% CI, 1.03 to 1.10). They also reported that the associated risk

Table 1. Nonhormonal agents used as therapy for hot flashes

Agent	Dose (mg/d)	Duration of dosage	Efficacy	Reference no.
Black cohosh	16–127	Up to 12 mo	26% reduction in hot flashes	[27]
Clonidine	0.1	8–12 wk	20% reduction in hot flashes	[28]
Fluoxetine	20	9 wk	50% decrease in hot flashes	[29]
Paroxetine	20–40	6–12 wk	33%–67% reduction in hot flash frequency	[30]
Soy	40–164	7–12 wk	Relatively short; long-term efficacy unknown	[31]
Venlafaxine	37.5–150	4–12 wk	Median hot flash frequency decrease by 7.6 hot flashes/day	[32]
Gabapentin	300	12 wk	45% reduction in hot flashes	[33]

of breast cancer increased with advanced age, potentially attributed to relatively longer HRT use. Moreover, the association between HRT use and breast cancer progressively diminished with increasing years of HRT cessation.

NON-HORMONAL OPTIONS

In accordance with the numerous reported toxicities associated with HRT, women are persistently inquiring about medical alternatives to HRT in endeavoring to attenuate their menopausal symptoms. Neurotransmitter modulators, namely selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine, fluoxetine) have been considered viable alternatives to hormone therapy [21-23]. Gabapentin, an anticonvulsant, and clonidine, an antihypertensive, have also been utilized to mitigate the frequency and severity of menopause-associated vasomotor symptoms by approximately 70% [24,25]; however, the precise mechanism of action inherent in these medications that attenuates patient symptoms remains indeterminate [23]. Soy and herbs have additionally conferred a reported beneficial effect in managing menopausal symptoms [26]. Please refer to Table 1 for a list of nonhormonal agents used as therapy for hot flashes [27-33].

CONCLUSION

HRT was routinely used in the 1990's to attenuate menopausal symptoms and currently, greater than 40% of women in the United States are prescribed this treatment [34]. Moreover, HRT reduces symptoms by 75% in the management of vulvovaginal atrophy, a urogenital condition that occurs in approximately 40% of postmenopausal breast cancer patients following treatment [35]. The combined results from the aforesaid HRT trials are varied, and thus, confound an unequivocal approach to treating menopausal symptoms. Conversely, when endeavoring to assess the risks associated with HRT, we recognize the disadvantages of untreated vasomotor symptoms, which can impair quality of life and diminish work productivity [36]. Perhaps, before initiating HRT, the physician and patient should thoughtfully engage in discourse that incorporates the individual's clinical symptoms and attendant risk profile.

ACKNOWLEDGMENTS

This study was supported by the Women's Cancer Research Foundation, Joan and Len Rullo, in memory of Elizabeth Johnson, and Susan Berg.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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