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Combined conjugated esterified estrogen plus methyltestosterone supplementation and risk of breast cancer in postmenopausal women

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ABSTRACT

Objectives: Testosterone supplementation is being prescribed increasingly to treat symptoms of hormone deficiency in pre- and postmenopausal women; however, studies of the association of testosterone therapy, alone or in combination with estrogen, with risk of breast cancer are limited. The current study assessed the association of combination conjugated esterified estrogen and methyltestosterone (CEE + MT) use and breast cancer risk in postmenopausal women in the Women's Health Initiative (WHI).
Study design: At Year 3 of follow-up, women in the WHI observational study ($N = 71,964$) provided information on CEE + MT use in the past two years, duration of use, and the brand name of the product. In addition, in each of years 4–8, women were asked whether they had used CEE + MT in the previous year. After 10 years of follow-up, 2832 incident breast cancer cases were identified. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of CEE + MT use (irrespective of use of other hormones) and of exclusive CEE + MT use in relation to breast cancer risk.
Results: Neither CEE + MT use nor exclusive use of CEE + MT was associated with risk: multivariable-adjusted HR 1.06, 95% CI 0.82–1.36 and HR 1.22, 95% CI 0.78–1.92, respectively. Among women with a natural menopause, the HR for exclusive use was 1.32 (95% CI 0.68–2.55). There was no indication of an association when repeated measures of CEE + MT use were included in a time-dependent covariates analysis.
Conclusion: The present study, the largest prospective study to date, did not show a significant association of CEE + MT supplementation and risk of breast cancer.

1. Introduction

Female sexual dysfunction and hypoactive sexual disorder are prevalent in postmenopausal women and are associated with reduced levels of endogenous testosterone [1]. A survey of prescriptions written by U.S. physicians revealed that 2 million prescriptions for testosterone for women were written in 2006–2007 [1]. This figure represents an increase since 2004. Furthermore, 21% of prescriptions for branded male testosterone products were written for women [1].

Combination oral esterified estrogen plus methyltestosterone (CEE + MT) has been widely used in the United States since the 1970s, although it has not been approved by the Food and Drug Administration (FDA) [2–4]. It is marketed for treatment of hot flashes [3]. The most commonly used products contain 1.25 mg of esterified estrogens and 2.5 mg of methyltestosterone

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(introduced in 1964) and 0.625 mg esterified estrogens and 1.25 mg methyltestosterone (introduced in 1974) [2]. Because these products contained relatively high dosages of estrogen and testosterone, they have largely been replaced by non-oral preparations, particularly the transdermal patch [5]. Whether oral CEE + MT therapy influences a woman's risk of breast cancer is unknown [6–14].

There is suggestive evidence that the risk of breast cancer may vary according to the balance between estrogen and testosterone (i.e., higher E-to-T ratio) [8]. Testosterone supplementation may have indirect effects on breast cancer risk by modifying the bioavailability of estrogen [9]. An increase in serum testosterone levels could lead to a decrease in the percent of estradiol bound to sex hormone-binding globulin (SHBG), thereby increasing risk [10,15]. On the other hand, experimental evidence indicates that testosterone has an inhibitory influence on the mitogenic and cancer-promoting effects of estrogen in breast cells and enhances apoptosis via the androgen receptor [11,12]. These findings are further supported by experiments in animals, including primates, that demonstrate that testosterone down-regulates cell proliferation at the molecular level [16,17].

Two recent prospective epidemiologic studies [6,7] have reported positive associations of combined estrogen plus testosterone supplementation (E + T) with risk of breast cancer. Tamimi et al. [7] found that the risk of breast cancer was 1.8-fold greater among current users of estrogen plus testosterone therapies than among never users of postmenopausal hormones, and a previous analysis of the Women's Health Initiative (WHI) [6] reported a non-significant positive association based on 35 exposed cases. In contrast, two prospective studies involving other testosterone preparations (implants and patch) showed no increase in risk [8,14].

Given the dearth of prospective studies, we reexamined the association of CEE + MT supplementation and breast cancer risk in the WHI observational study with an additional 5.3 years of follow-up and roughly five times as many incident breast cancer cases and a total of 75 exposed cases.

2. Methods

The Women's Health Initiative (WHI) is a large, multi-center, multi-pronged prospective study designed to advance our understanding of the determinants of major chronic diseases in older women [18]. It is composed of a clinical trial component (CT) and an observational study (OS). Women between the ages of 50 and 79 and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998. Details of the design and reliability of the baseline measures have been published [18,19].

Self-administered questionnaires, completed at study entry, were used to collect information on demographics, medical, reproductive and family history, and on dietary and lifestyle factors, including smoking history, alcohol consumption, and recreational physical activity. Three questions regarding the use of CEE + MT were asked of OS participants in the Year 3 follow-up: (1) "In the past 2 years, did you use female hormone PILLS prescribed by a doctor which contained both ESTROGEN and TESTOSTERONE COMBINED in the same pill?"; (2) "In the past 2 years, how many months did you use COMBINED female hormone pills which contained both ESTROGEN and TESTOSTERONE?"; (3) "In the past 2 years, what type of COMBINED ESTROGEN and TESTOSTERONE pill did you use the longest?" In succeeding annual questionnaires (years 4–8), the same questions were asked with reference to the previous year. Questions about use of other hormones (estrogen and progesterone) distinguished between products containing estrogen alone (E), progesterone alone (P), or both (E + P).

At baseline (Year 0), current use of medication was assessed through direct review of participants' medication bottles. At Year 3, women in the WHI OS were asked to record all current medications and were asked to bring in any new medications at the Year 3 clinical visit. Information recorded included the product name, mode of use (transdermal patch, injection, pill), and the dose. We examined all responses containing the words "androgens," "testosterone," or "estrogen plus testosterone" in the current medications questionnaire to determine to what extent other testosterone preparations were used.

2.1. Ascertainment of breast cancer

New breast cancer diagnoses were updated annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of a breast cancer diagnosis were verified by centralized review of medical records and pathology reports by trained physician adjudicators [20].

2.2. Analytic sample

Of the 93,676 women enrolled in the OS at baseline, 82,560 completed the Year 3 questionnaire (Fig. 1). We excluded respondents with a history of breast cancer prior to Year 0 ($N = 5303$), those who reported a breast cancer diagnosis between Year 0 and Year 3 ($N = 1297$), and those with missing information on hormone use at Year 3 ($N = 3996$), leaving 71,964 women in the analysis. We proceeded to create two datasets. Dataset #1 ("CEE + MT use" – whether or not other hormones were used) included all women with information on use (yes, no) of hormones at Year 3 ($N = 71{,}964$). In this dataset we compared users of CEE + MT, regardless of whether or not they had used other hormones ($N = 1714$: 75 cases and 1639 non-cases) to women with no hormone use or who only used hormones other than CEE + MT (i.e., E or E + P) ($N = 70{,}250$: 2757 cases and 67,493 non-cases). A second dataset (dataset #2 – "exclusive CEE + MT use") was created by further restricting dataset #1 to women who used CEE + MT only or who reported no hormone use at Year 3 ($N = 30{,}889$). In this dataset we compared exclusive users of CEE + MT reported at Year 3 ($N = 497$: 22 cases and 475 non-cases) to women with no reported hormone use at Year 3 ($N = 30{,}392$: 1041 cases and 29,351 non-cases). Over a mean follow-up of 10 years, as of December 11, 2012, 2832 incident cases of invasive breast cancer were identified in dataset #1 and 1063 cases were identified in dataset #2.

2.3. Statistical analysis

We used Cox proportional hazards models to assess the association of use of CEE + MT supplementation at the Year 3 visit and subsequent risk of breast cancer in both datasets. Women who did not develop breast cancer during follow-up were censored at death, cancer diagnosis (other than the index cancer), or end-of-follow-up, whichever occurred earliest. Measures of exposure included: CEE + MT supplementation in the past 2 years (yes, no); duration of use (no. of months); and type of CEE + MT preparation (Estratest, Estratest HS, other). We computed age-adjusted hazard ratios and multivariable-adjusted HRs. Owing to the large number of covariates and the relatively small number of exposed cases, we dichotomized categorical covariates and used continuous variables wherever possible to maximize statistical power. We used a number of alternative models, adjusting for a range of breast cancer risk factors. These gave similar results, and we present the results of the model including the following covariates: age (continuous), family history of breast cancer in a first degree relative (yes, no), previous breast biopsy (yes, no), number of mammograms in past 5 years (≥ 4, <4), pack-years of smoking (continuous), and body mass index