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Letter to the Editor

Estrogen Use and Breast Cancer Increases

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The Women's Health Initiative (WHI) clinical trials 24-year follow-up study found increases in breast cancer and mortality with combined progestin/estrogen hormone therapy (HT) but reduced risks with estrogen-only HT [1]. The latter finding is dubious especially as HT use seems to be unknown during the long follow-up period [1].

Originally 27,347 postmenopausal women aged 50-79 years were enrolled from 1993 to 1998 when 16,608 women with a uterus received combined HT or placebo and 10,739 women with a prior hysterectomy were given 0.625 mg/d of conjugated equine estrogen (CEE) alone or placebo. Confoundingly, 47.8% of the volunteers were current or past users of HT at a mean age of 63.6 years. Also, 43% of women had previously taken oral contraceptives and 26% had taken HT for ≥ 10 years before randomization while 10% of the placebo group took HT during the trial.

The WHI combined HT trial was stopped after 5.6 years in 2002 because of increases in breast cancer, venous thromboembolism, coronary heart disease (CAD) and stroke. The WHI estrogen-only HT trial was stopped in 2004 after 7.2 years because of increases in strokes and venous thrombosis. Both studies found increases in all cardiovascular events and gall bladder disease.

Beral and colleagues observed in 2003 that the WHI studies found "remarkably similar" increased risks of estrogen HT-associated breast cancer as the Million Women Study (MWS) and the worldwide Collaborative Group's study in which 80% of HT users used estrogen-only preparations. The estimated excess incidence of breast cancer with estrogens increased from 2 to 6 per 1000 users in the Collaborative study and from 1.5 to 5 per 1000 users in the MWS for 5 and 10 years of use. Longer use of either estrogen HT or combination HT for up to 10 years caused 3x more breast cancer compared with more than 5 years of use [2].

The 2019 Collaborative Group on Hormonal Factors and Breast Cancer study of 108,647 postmenopausal women developing breast cancer at a mean age of 63 years concluded that all types of HT were associated with increased risks of developing breast cancer. Half of the women had used HT, usually from ages 40-59 years. The study reported increased risk of breast cancer and breast cancer mortality with estrogens, progesterone, progestin and estrogen combinations especially with use for longer than 5 years [3].

After early stoppage of the WHI randomized trials in 2002 and 2004, the fall in HT use in hormone taking countries matched declines in breast cancer incidences and mortality in older women [4]. Estrogen positive breast cancers particularly decreased [5]. HT use has fallen from 36 million to 12 million women in Western countries in the past two decades [3].

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It is important to know which women took estrogen only HT after the original WHI studies were terminated prematurely. It would be a pity if breast cancers increased following this latest prolonged WHI follow-up.

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