Letters

COMMENT & RESPONSE

Estrogen-Only Hormone Therapy and Dementia

To the Editor A recent study[1] reported that estrogen-only menopausal hormone therapy in women who underwent hysterectomy without oophorectomy was associated with an increased dementia rate vs nonuse. This article has several limitations that should be considered when interpreting the study's findings.

First, it is unclear why this study focused on women with hysterectomy without oophorectomy. Perhaps the authors excluded women with oophorectomy because this procedure immediately triggers menopause. However, hysterectomy without oophorectomy can also induce ovarian failure,[2] possibly due to interruption of ovarian blood supply. Without knowledge of hormone levels or reproductive status after hysterectomy, it remains unknown whether rates of early ovarian failure differed between estrogen-only hormone therapy users and nonusers. This is important because early loss of endogenous estradiol increases dementia risk,[3] and estrogen-only hormone therapy use may be more likely to be prescribed after early ovarian failure. Other differences that could contribute to greater dementia risk in women prescribed estrogen-only hormone therapy include vasomotor symptoms, cognitive difficulties, and sleep disturbances. Notably, randomized trials that limited residual confounding have generally demonstrated that estrogen-only hormone therapy has no significant effect on dementia risk.[4]

Another concern is that this study[1] did not precisely consider timing of estrogen-only hormone therapy relative to menopause because initiating treatment proximal to menopause may be associated with decreased dementia risk, whereas later use of estrogen-only hormone therapy did not provide this benefit and may even be harmful.[4] Notably, hysterectomy without oophorectomy can accelerate ovarian failure by approximately 4 years.[5] The median age at hysterectomy in this study[1] was 43 years, whereas the median age at estrogen-only hormone therapy initiation was 53 years, reflecting a potentially large gap between menopause and estrogen-only hormone therapy initiation.

This study[1] did include subanalyses in women who used estrogen-only hormone therapy until age 55 years or younger, assuming use in this group would be within the clinically recommended window. While the association with dementia rate persisted, data on age at hysterectomy and age at estrogen-only hormone therapy initiation in this subgroup were not reported. The inability to account for timing of estrogen-only hormone therapy relative to menopause raises the possibility that the higher dementia rate in estrogen-only hormone therapy users was driven by delayed estrogen-only hormone therapy initiation.

These considerations suggest that the association between estrogen-only hormone therapy and dementia may not be causal.

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