Estrogen linked with lower dementia risk when taken in middle age, higher risk later in life

February 2 2011

Estrogen therapy taken around the time of menopause was associated with a lowered risk of dementia in old age, but when taken in late life was linked with an increased dementia risk, according to a study led by a physician at the San Francisco VA Medical Center and the University of California, San Francisco.

Kristine Yaffe, MD, chief of geriatric psychiatry at SFVAMC, is principal investigator of the retrospective study, which analyzed the health records of 5,504 post-menopausal women who were members of the Kaiser Permanente Medical Care Program of Northern California. The study appears in the January 2011 issue of *Annals of Neurology*.

Yaffe, who is associate chair for clinical and translational research in psychiatry and professor of psychiatry, neurology, and epidemiology and biostatistics at UCSF, said she conceived the study in an attempt to resolve contradictory evidence on the neuroprotective effects of estrogen . “In animal models and molecular studies, it looked as if estrogen had beneficial effects on the brain, especially if administered early,” she said, “while at the same time, research in humans indicated that estrogen therapy was associated with an increased risk of dementia.”

In particular, she said, the Women’s Health Initiative, a nationwide study funded by the National Institutes of Health, showed significant links between estrogen therapy and dementia, as well with as a host of other

serious health problems, including breast cancer, stroke, and cardiovascular disease.

“Nonetheless,” said Yaffe, “some scientists have wondered if the problem with estrogen and dementia is that you have to expose women to hormones at a certain critical period, during and just after menopause – and that older age is too late.”

She decided to test this hypothesis, known as the “critical window theory,” by looking at more than 40 years’ worth of data on the Kaiser members: a health survey taken between 1964 and 1973, when the women were middle aged; the women’s pharmacy records from 1994 to 1998; and their patient diagnoses from 1998 to 2008. “It was the best way I could conceive of to look at the question of mid-life versus late-life exposure to hormone therapy,” said Yaffe, “since no one is going to fund a 30-year trial on this question.”

The results, she said, “seem to confirm the critical window hypothesis.” Women who took estrogen in mid-life but not in late life had a 26 percent decreased risk of developing dementia in old age compared with women who had never taken estrogen at any age, whereas women who took estrogen in late life but not in mid-life had a 48 percent increased risk of dementia compared with non-estrogen-taking women.

Women who took estrogen in both mid-life and late life had the same dementia risk as women who never took it.

According to Yaffe, the study is important for two reasons: “First, it replicates the results of the Women’s Health Initiative, in that it shows that estrogen exposure in late life increases your risk of dementia, and that women should not take estrogen at that time in hopes of reducing dementia.”

Second, she said, “it suggests that if you’re exposed to estrogen only around menopause, and not in later life, it may be protective. We aren’t sure why, but studies in animal models indicate that during menopause, estrogen may increase neuronal health and reduce the changes in the brain seen with Alzheimer’s disease.”

Yaffe emphasized that she is not endorsing hormone therapy for post-menopausal women. “This was an observational study, not a drug trial,” she cautioned, “so we cannot say for sure that mid-life estrogen is responsible for the protective effects we observed. It is suggestive, but it is not proof.”

Yaffe said that “while the known health risks of hormone therapy must be acknowledged, I will note that cancer, stroke, and cardiovascular disease tend to be age-related. It may be that if we restrict hormone therapy to a year or two around the menopause transition, and then stop it, it may not increase the risk for these other things. We just don’t know.”

Yaffe’s conclusion: “We need to go back and think carefully about estrogen. My hope is that this study will help open the door to other studies – that it will tell funding agencies that the question is more complicated than we thought.”

Provided by University of California, San Francisco