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Chapter 3

Estrogen therapy – relationship to longevity and prevalent dementia in the oldest-old: the Leisure World Cohort Study and the 90+ Study

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Editors' introduction

To our knowledge, the study by Kawas et al. *is the first observational study to describe a significant increase of dementia risk in older women who had been using hormones for five to nine years. The Leisure World Cohort Study was initiated in 1981 and consisted of women residing in a California retirement community (N = 8,801) who had completed a postal survey including details of estrogen therapy [ET]. After 22 years of follow-up, ET users (ever) had a 10% lower age-adjusted mortality than lifetime non-users. This risk was further decreased with increasing duration, but was not related to dose (0.625 mg vs. 1.25 mg). The relationship did not significantly change when adjusted for potential confounders, including exercise, body mass index, smoking, and medical histories related to mortality. The 90+ Study was initiated to directly examine surviving members of the cohort to determine clinical and functional status. Research participants who were alive and aged 90 and older on January 1, 2003 were invited to participate (N = 706 women, 90–106 years old). Prevalence of all-cause dementia was 45% in these women, but was not lower in ever-users of estrogen. Somewhat surprisingly, women who had used estrogen for five to nine years appeared to have an increased prevalence of dementia (odds ratio (OR) = 2.02, 95% CI 1.17–3.45), but longer or shorter duration of use was not associated with increased or decreased risk. This chapter discusses these results with regards to timing of exposure and age.*

Introduction

In recent years, randomized clinical trials with postmenopausal estrogen therapy (ET) found increased risks of dementia, coronary heart disease, stroke, and venous thromboembolic disease among women assigned to conjugated equine estrogens alone or in combination with medroxy-progesterone acetate compared with placebo [1–5]. These results contradict the numerous observational studies that suggested that use of estrogens is associated with lower risk of dementia, cognitive decline, other conditions, and mortality. The randomized trials minimized confounding, an important consideration since women who take estrogens undoubtedly differ from those who do not in many lifestyle factors, use of health services, and other ways. However, the randomized studies were of relatively short duration and could not address issues regarding long-term use or the long-term effects of more limited perimenopausal use. For practical considerations, it is unlikely that randomized trials involving large numbers of women with follow-up of 15 years or more will be conducted. In this chapter, we describe results from a 22-year observational study of ET, mortality, and dementia. Long-term observational studies such as the Leisure World Cohort Study and the 90+ Study will continue to contribute valuable data that will complement those from clinical trials.

Study cohorts

In the early 1980s, investigators from the University of Southern California established a prospective cohort study of 8,877 postmenopausal women with the goal of studying the risks and benefits of ET [6]. After 7.5 years of follow-up, women who had used estrogens had 20% lower risk of death compared to

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women who had not used estrogens. This cohort provides the foundation for our investigations of the relationships between estrogen use and longevity and dementia in older women. With follow-up extended to 22 years, we investigated estrogen use and menstrual factors in relation to long-term mortality in the Leisure World Cohort Study. With additional neurological and neuropsychological examinations for dementia as part of the 90+ Study [7, 8] we also investigated estrogen use in relation to prevalent dementia in these women aged 90 years and older.

Estrogen therapy and longevity: the Leisure World Cohort Study

For the Leisure World Cohort Study, a health survey was mailed to all residents who owned homes in Leisure World Laguna Hills, a California retirement community, on June 1, 1981; June 1, 1982; June 1, 1983; and October 1, 1985. Of the 13,978 residents who returned the questionnaire and constitute the Leisure World Cohort, 8,877 are women. Reflecting the local community, they are predominantly white, well-educated, and upper middle class. The health survey asked demographic information, brief medical history, personal lifestyle habits, and use of medications, including postmenopausal ET, and other menstrual factors. The women were classified as "ever" or "never" users of ET. Duration of ET is the total number of years during which any ET was taken. Dose of ET is the dose of the oral conjugated estrogens taken for the longest period.

These female cohort members, the subjects for our study of estrogens and longevity, were followed to June 1, 2003, by periodic resurvey, review of hospital discharge records, and search of death indexes. Age-adjusted risk ratios (RRs) for death were obtained using proportional hazard regression analysis and controlling for potential confounding baseline factors (age, smoking, exercise, body mass index, and histories of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer). After excluding 27 women who did not report their use of ET and 49 women with missing information on the potential confounding variables, data of 8,801 women were analyzed.

We found no association between death and most menstrual-related variables. Mortality was unrelated to age at menarche, age at first child, and type of menopause (natural vs. artificial). In addition, neither practice of breast self-examination nor having had a mammogram reduced risk of death.

However, as shown in Fig. 3.1, ET users had a 10% lower mortality rate compared to non-users [9]. Consistent with the time period, the majority of ET in these women was in the form of oral conjugated equine estrogens (CEE) without opposing progestin. Lower dose (0.625 mg) CEE users had a slightly better (but not statistically significant) survival than higher dose (>1.25 mg) users. Users of ET experienced a decreasing mortality rate with increasing duration of use. In summary, after adjustment for multiple factors, women who used ET initiated in the perimenopausal period lived longer with the longest-lived being in the group who used estrogens the longest.

Estrogen therapy and longevity: previous studies

Although observational studies have consistently shown a 20–50% reduction in mortality among users of estrogens [10–15], the randomized clinical trials of short-term ET found no decrease in mortality among estrogen users in both primary and secondary prevention trials. In the secondary prevention trials, the risk of death was increased by 8–20%, although these associations were also not statistically significant. In these trials, the RRs were 1.08 (95% CI = 0.84–1.38) during 4.1 years of follow-up in the Heart and Estrogen/Progestin Replacement Study (HERS) [5], 1.10 (95% CI = 0.91–1.31) during 6.8 years of observations in HERS and HERS II [16], and 1.2 (95% CI = 0.8–1.8) in the Women's Estrogen for Stroke Trial (WEST) [17]. In the primary prevention trials of the Women's Health Initiative (WHI), estrogens and placebo groups also did not differ in short-term mortality for combined estrogens–progestin during five years of follow-up (RR = 0.98, 95% CI = 0.82–1.18) [3] or for the estrogens-alone therapy with an average of 6.8 years of follow-up (RR = 1.04, 95% CI = 0.88–1.22) [4].

In these clinical trials, ET was initiated in women well past menopause (average age in HERS was 67 years; WEST, 71 years; WHI, 71 years). Interestingly, HERS data suggested that ET and risk of coronary heart disease (CHD) might change over time. Coronary heart disease events (non-fatal myocardial infarctions and CHD deaths) were increased in ET users in year 1 after randomization (RR = 1.52, 95% CI = 1.01–2.29). Over time, however, CHD risk became similar in both groups, and in years 4 and 5 a non-significant

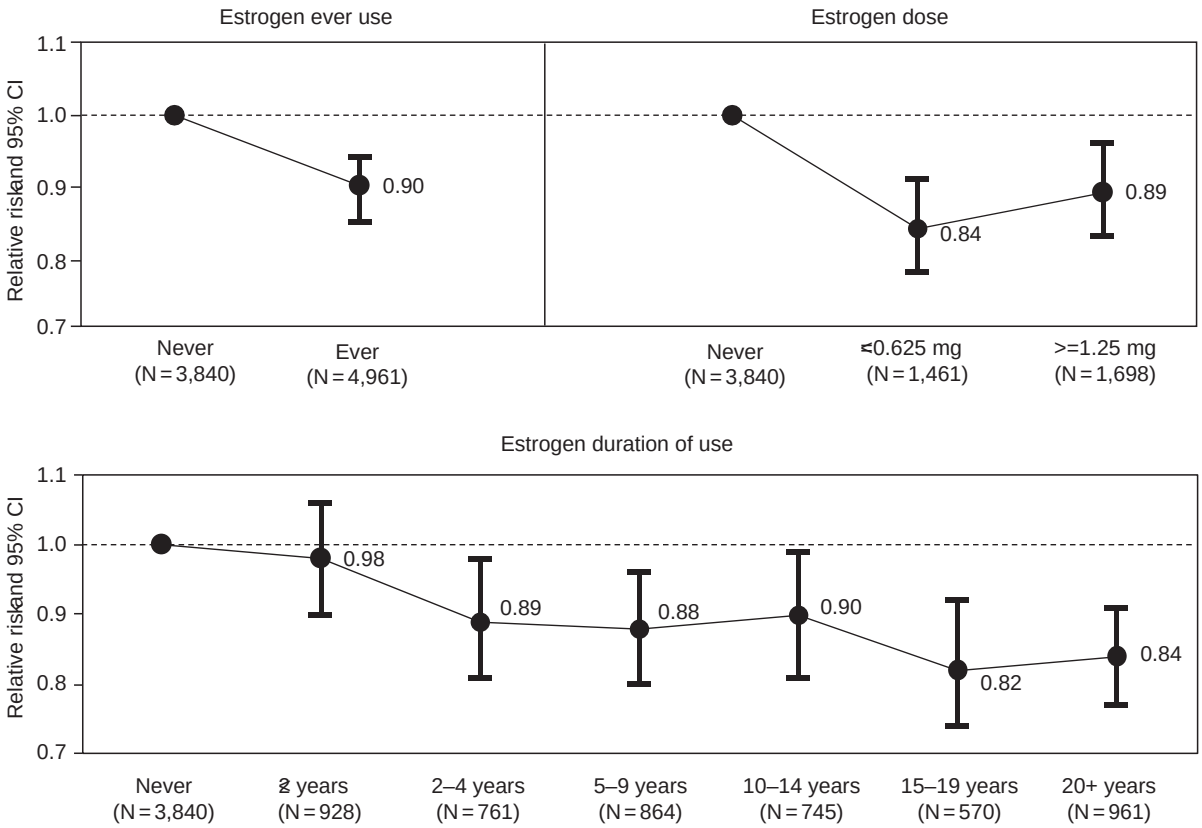

Fig. 3.1 Relative risk of dying by estrogen therapy use, dose, and duration: the Leisure World Cohort Study 1981–2003.

protective trend was seen for those randomized to ET (RR = 0.67, 95% CI = 0.43–1.04). In fact, a similar trend of protection over time was observed for all events of interest, except venous thrombotic events, which remained elevated in ET users.

Estrogens and dementia: the 90+ Study

Participants in the Leisure World Cohort who were alive and 90 years or older on January 1, 2003 comprise the subjects of the 90+ Study (N = 1150, 77% women). As of July 1, 2006, 941 participants had been recruited into the study. These participants are followed longitudinally every six months with in-person neuropsychological evaluations and neurological examinations, telephone interviews, and informant questionnaires. We investigated the relationship between prevalent dementia in the oldest-old and use of estrogens reported 21 years earlier in the 706 women of the 90+ Study. Estrogen use was reported on their baseline Leisure World Cohort health survey in the early 1980s. A determination of dementia was done using in-person examinations as well as telephone and informant questionnaires and applying *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) criteria for dementia or age- and education-specific cutpoints on screening tests [18]. Adjusted odds ratios (ORs) for dementia were obtained using logistic regression analysis and controlling for potential confounding factors (age, education, and smoking) measured at the baseline evaluation of the 90+ Study.

The average time between the baseline Leisure World Cohort health survey and the baseline evaluation of the 90+ Study was 21 years (range: 15–22 years). The average age of these women at the 90+ Study baseline evaluation was 93 years (range: 90–105 years). Of the 706 women in the study, 317 (45%) were determined to have dementia at their 90+ Study baseline evaluation. Estrogen therapy showed little, if any, relationship with dementia prevalence

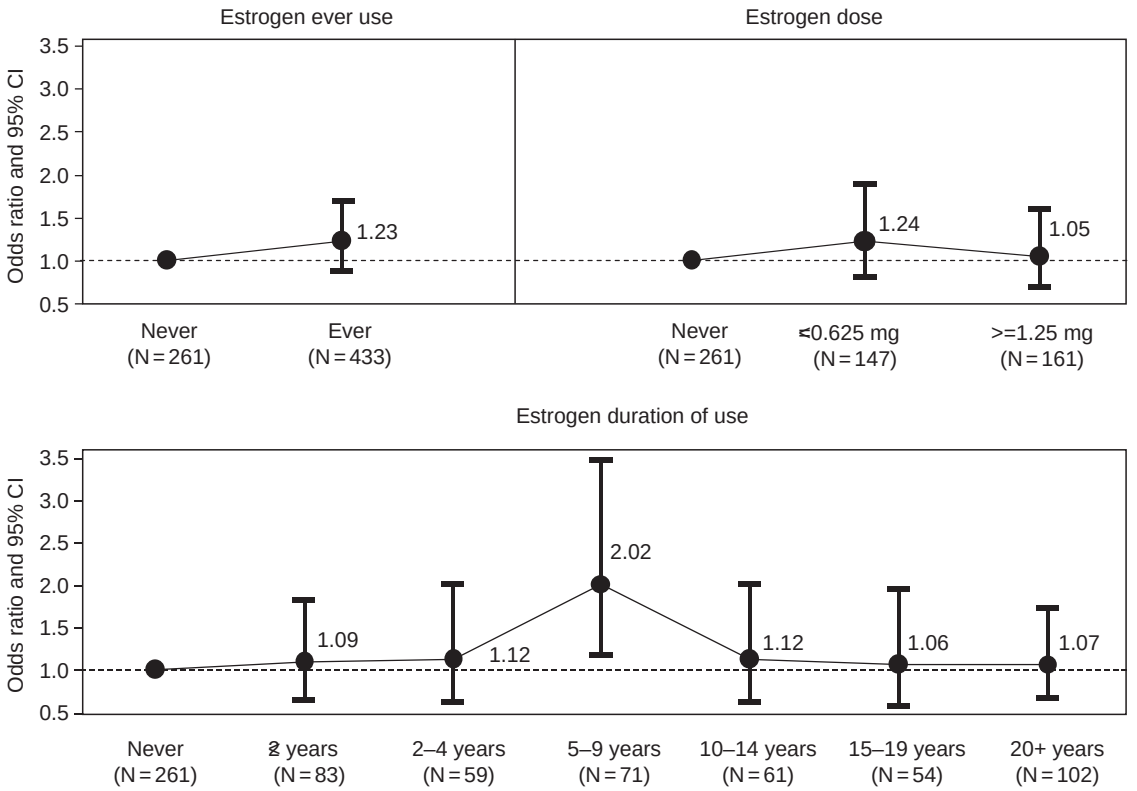

Fig. 3.2 Odds ratio of prevalent dementia by estrogen therapy use, dose, and duration: the 90+ Study 2003.

at the baseline visit (Fig. 3.2). After adjustment for age, education, and smoking, neither ever use of ET nor dose of ET was associated with prevalent dementia. Duration of ET was also generally unrelated to prevalent dementia. Only women who had used ET for 5–9 years had increased odds of dementia (OR = 2.02, 95% CI = 1.17–3.45). Interestingly, as discussed below, this is somewhat similar to the duration of use in the WHIMS randomized trial of dementia prevention, which showed a paradoxical increased risk for dementia after a mean exposure of 4.5 years.

Estrogens and dementia: previous studies

Although not all studies agree, most published observational studies on the effects of ET on dementia have reported a decreased risk of dementia and Alzheimer's disease (AD) among users of estrogens compared to non-users. Initial results regarding ET and AD were from case-control or cross-sectional studies and were somewhat inconclusive, with some studies finding a significant decrease in risk with ET [19–21], and others finding no association [22–27]. The first prospective study of estrogens and AD was published in 1994 and reported results from the Leisure World Cohort Study [28]. In this report, AD and related dementias occurred less often in women using ET compared to non-users. Furthermore, this study showed a significant dose and duration effect, with AD risk decreasing with increasing dose and duration. Subsequently, other prospective studies also found a lower risk of AD and dementia among ET users [29–32] with many finding greater effects with longer durations of use [29, 31]. A 1998 meta-analysis of ET and AD did not find a significant risk reduction when combining data from case-control studies but did find a 52% reduction in risk of AD among ET users when combining the results of two prospective cohort studies [33]. A more recent meta-analysis of 12 case-control and cohort studies also found a reduction in the risk of dementia among ET users compared to non-users when combining the results of 12 case-control and cohort studies [34].

Results from randomized clinical trials described above are in sharp contrast with results from the observational studies. In 2003, the Women's Health Initiative Memory Study (WHIMS) reported results from over 7,000 women aged 65–79 who were randomized to conjugated equine estrogens (CEE) alone, conjugated equine estrogens plus medroxyprogesterone acetate (MPA), or placebo and who were followed for the development of dementia and memory loss. Women in the CEE+MPA group had twice the risk of developing dementia when compared to the placebo group (hazard ratio [HR] = 2.05, 95% CI = 1.21–3.48) [1]. Although the risk of dementia among the CEE-alone group was not significantly increased compared to placebo (HR = 1.49, 95% CI = 0.83–2.66), when the data from the two CEE arms were pooled, the risk of dementia was significantly increased (HR = 1.76, 95% CI = 1.19–2.60) [2]. The average time between randomization and last examination was 5.2 years in the CEE-alone trial, 4.1 years in the CEE+MPA trial, and 4.5 years in the pooled data. These women were followed up to about 8 years, and a few were followed beyond 8 years. Considering the results of observational and randomized studies, the possibility is suggested that ET and the risk of dementia may vary by timing of initiation and duration of therapy.

In the 90+ Study, the OR of prevalent dementia for women who used ET for 5–9 years differed significantly from that of non-users, but it is difficult to explain biologically such a duration-specific result. Moreover, studies of prevalent cases may detect factors relevant to the duration of disease rather than risk. Finally, there is always the concern of finding a spurious significant result when doing multiple comparisons. We are in the process of prospectively examining estrogen use and risk of developing dementia in the 90+ Study (incident cases), which will hopefully provide additional insight into the issues of timing and duration.

Conclusion

In the Leisure World Cohort Study, we found use of ET by women was associated with longer life. Our results are consistent with numerous other observational studies that have suggested mortality benefits for women who start estrogen therapy in the perimenopausal period. Moreover, most observational studies have also shown estrogen-related benefits in regards to dementia. In contrast, randomized trials, with ET generally initiated later in life, have shown no benefits in regards to mortality and dementia and have even suggested an increase in risk of dementia and AD. The effects of timing (duration of use and initiation of exposure) require further investigation because it is possible that the benefits and risks of ET exposure change with time. Exposure to ET in the perimenopausal period is likely to have different effects than novel exposure later in a woman's life, as was studied in the large randomized clinical trials that showed increased risks for dementia. Long-term randomized clinical trials would be ideal to explore the issues of timing further, but these studies are unlikely to be conducted for practical and ethical reasons. It is always a concern in observational studies that factors other than estrogens may be responsible for the observed benefit (confounding). Although observational studies have shown beneficial associations for women with exposure to estrogens, the available evidence at present does not support a role for the clinical use of estrogens in the prevention of dementia. It is likely that the risks and benefits of ET change in women over time and at different ages, formulations, doses, and durations of ET. More research in the clinic and laboratory is necessary to understand more fully the effects of hormonal factors, including the putative role of estrogens in longevity and the prevention of dementia and other age-related conditions.

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