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Paganini-Hill, A

Corrada, MM

Kawas, CH

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Prior endogenous and exogenous estrogen and incident dementia in the 10th decade of life: The 90+ Study

Annlia Paganini-Hill[1], **Maria M Corrada**[1,2], **Claudia H Kawas**[1,3]

[1]Department of Neurology, University of California, Irvine, California, USA

[2]Department of Epidemiology, University of California, Irvine, California, USA

[3]Department of Neurobiology & Behavior, University of California, Irvine, California, USA

Abstract

Objective—To investigate the association of endogenous and exogenous estrogen exposure with risk of incident dementia in the oldest-old (age 90+ years).

Methods—Participants were part of *The 90+ Study*, a longitudinal study begun in 2003 of aging and dementia among people aged 90+ years. Menstrual, reproductive and menopausal data were collected in the 1980s as part of the population-based *Leisure World Cohort Study*. Cognitive status at baseline was determined from an in-person neurological evaluation with biannual follow-up through June 2019. Hazard ratios (HRs) of dementia associated with estrogen-related variables were estimated using Cox regression analysis. No adjustment was made for multiple comparisons.

Results—424 women without dementia at baseline had at least 1 follow-up evaluation. Mean age was 68.5 at enrollment in the *Leisure World Cohort Study*, 93.2 at enrollment in *The 90+ Study*, 96.5 at last follow-up. During follow-up (mean 3.4 years) dementia was diagnosed in 209 (49%). No individual menstrual, reproductive, menopausal or estrogen replacement variable was associated with risk of incident dementia after age 90. However, women with a high endogenous estrogen exposure index (summarizing exposure from menarche to menopause) had a non-significant 25% lower risk (HR=0.75, 95% CI 0.53–1.06).

Conclusions—Prior exposure to estrogen, endogenous or exogenous, had little effect on risk of dementia in the 10th decade of life.

Keywords

dementia; incidence; estrogen; cohort; oldest-old; women

Introduction

Exposure to endogenous or exogenous estrogen may protect against dementia, but evidence is equivocal. In women, endogenous estrogen exposure occurs primarily during the

Corresponding author: Annlia Paganini-Hill, apaganin@uci.edu, Clinic for Ageing Research and Education, 24361 El Toro Road #150, Laguna Woods, CA 92637, Phone: 949-768-3635; Fax: 949-768-7695.

Potential Conflict of Interest

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reproductive phase. Estrogen levels rise during pregnancy, but fall postnatally, particularly with breastfeeding, and are lower after a first pregnancy than in nulliparous women. Earlier menarche, null or lower parity, and older age at birth of first child, and later menopause are therefore proxy indicators of lifetime endogenous estrogen exposure [1, 2]. Few studies have examined the effects of endogenous estrogen exposure and incident dementia. In case-control studies, Alzheimer's Disease (AD) was associated with increasing age at menarche [3], increasing number of pregnancies [4], childlessness (inversely) [5]; and decreasing age at natural menopause [6]. However, the large population-based Rotterdam cohort study of 3601 postmenopausal women aged 55 years or older and followed for a median of 6.3 years (21,046 person years) had findings counter to these results [7]. Women with natural menopause and more reproductive years had an increased risk of dementia (RR = 1.78 for highest vs lowest quarter). In the largest prospective cohort study of 8466 women (the 10/66 population-based cohort with sites in Cuba, Dominican Republic, Puerto Rico, Venezuela, Peru, Mexico, and China), no association was observed between incident dementia and ages at menarche, birth of first child, and menopause; nulliparity; or index of cumulative endogenous estrogen exposure [8].

Some evidence supports a role of estrogen deprivation following menopause in the pathogenesis of dementia and a protective effect of exogenous estrogen exposure [9, 10]. However, more recent studies [11] and a review and meta-analysis concluded that the existing heterogenous evidence does not support an association between prolonged exposure to exogenous estrogen and lower dementia risk [12].

We investigated the potential association of both endogenous and exogenous estrogen exposure on dementia risk in a population-based longitudinal cohort of the oldest-old (age 90+ years), the age group with the highest incidence of dementia [13].The study of reproductive and menstrual factors as they impact risk of hormone-sensitive cancers has increasingly relied on models that combine multiple markers into a single variable [14, 15] which provide greater predictive power than consideration of individual markers. Therefore, we calculated an estrogen exposure index across the span from menarche to menopause and explored its relationship with dementia.

Methods

Study Population

Participants were part of *The 90+ Study,* a longitudinal study of aging and dementia among people aged 90 years and older [16]. These subjects were originally members of the *Leisure World Cohort Study*, a population-based epidemiological health study established in the early 1980s of a California retirement community (Leisure World Laguna Hills) [17]. This cohort is composed of moderately affluent, highly educated, and health conscious individuals; two-thirds are women. Persons alive and aged 90 years and older on January 1, 2003 (n=1143); on January 1, 2008 (n=440); and on or after January 1, 2009 (n=521) were invited to participate in *The 90+ Study*. Of the 2104 eligible cohort members, 1622 joined *The 90+ Study*. Women numbered 1267.

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Estrogen Exposure

In the early 1980s a health survey was mailed to residents of Leisure World. This survey asked of the women: age at first menstrual period, ever pregnant, age at first child, number of children, age at last menstrual period, hysterectomy, age at hysterectomy, number of ovaries removed, age at first ovary removal, age a second ovary removal. Questions about estrogen replacement therapy asked for use of estrogens (separately for oral, injectable, cream or suppository) age started, current use, age stopped; for Premarin® (the most commonly used oral estrogen) all doses taken and that taken for the longest amount of time, and total number of years of Premarin®, other oral estrogens, injections, creams or suppositories.

In addition to calculating reproductive years (age at last menstrual period minus age at menarche), we developed an Endogenous Estrogen Exposure Index (EEEI) to include markers from menarche to the time of menopause with clear effects on estrogen levels. Those with increased estrogen exposure included early age at menarche, age at first child, later age at menopause and with decreased estrogen exposure included later age at menarche, parity, early age at menopause, oophorectomy. Simply stated, estrogen exposure starts at menarche, moves regularly to the first full term pregnancy (with a one-time increase) then drops below that seen in nulliparous women, starts declining at the time of perimenopause, and levels off at the time of natural menopause (last menstrual period). Oophorectomy causes an early drop in estrogen level. For our EEEI, we made several assumptions: (1) for women who had a natural menopause, age at menopause = reported age at last menstrual period, (2) for women who had a surgical menopause without bilateral oophorectomy before the age of 51, age at menopause = 51 (the average age at menopause in the US [18] and in this cohort), (3) for women who had a bilateral oophorectomy (unless it was after age 51), age at menopause = age at oophorectomy. Additionally, we assumed that the perimenopausal period starts about four years before menopause (generally mid- to late- 40s and ends at age at menopause[19]). If a women had no child, we made age at first child = age at start of perimenopausal period or age at bilateral oophorectomy. We then calculated

$$\begin{aligned} \text{EEEI} = {} & f_0 * (\text{age at first child} - \text{age at menarche}) \\ & + f_1 * (\text{age at perimenopause} - \text{age a first child}) \\ & + f_2 * (\text{age at menopause} - \text{age at perimenopause}) \\ & + f_3 * \text{number of children,} \end{aligned}$$

where the coefficients relate to the relative estrogen exposure during different periods with f_0=1.0 (after menarche), f_1=0.8 (drop after first birth), f_2=0.4 (drop during perimenopause, average from 0.8 to 0), f_3=1.4 (increase with each child). The value 0.8 was chosen for f_1 based on the finding of 22% lower estrogen levels in parous women compared with nulliparous women [20]. Estrogen levels increase during pregnancy especially during the last trimester; a five-fold increase for 3–4 months suggested a 1.4 increase for each pregnancy [21].

If a woman had bilateral oophorectomy before age 47, there is no perimenopausal period and

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$$\text{EEEI} = f_0 * (\text{age at first child} - \text{age at menarche}) + f_1 * (\text{age at oophorectomy} - \text{age a first child}) + f_3 * \text{number of children}.$$

Assessments

Participants in *The 90+ Study* were asked to undergo longitudinal in-person evaluations, either at the research office or at their home. The evaluation included a neurological examination (with mental status testing[22] and assessment of functional abilities[23] by a trained physician or nurse practitioner and a neuropsychological test battery that included the Mini-Mental State Examination (MMSE) [24]. For participants whose poor health, frailty, disability, or unwillingness did not allow an in-person evaluation, information was obtained by telephone or with informant. Participants evaluated by telephone completed the short version of the Cognitive Abilities Screening Instrument (CASI-short) [25]. For participants evaluated through informants, the Dementia Questionnaire (DQ) [26] was completed over the telephone. All participants (or their informants) completed a questionnaire that included demographics (including education), past medical history, and medication use. In addition, informants of all participants were asked about the participant's cognitive status and functional abilities using a mailed questionnaire. Evaluations were repeated every 6 months for in-person participants and annually for participants evaluated by telephone and through informants. The DQ was completed for all participants shortly after death.

Determination of Cognitive Status

For all participants included in this analysis, cognitive status at baseline was determined from an in-person evaluation, either a neurological exam (91%) or MMSE score (9%). Cognitive status at follow-up was also determined from an in-person evaluation for most participants (81%) [13]. However, when an in-person evaluation at follow-up was not possible, we used any available information in the following hierarchical order: (1) neurological exam, (2) MMSE, (3) informant questionnaires, and (4) CASI-short. The neurological examiner determined cognitive status applying Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia [27]. For the MMSE, we used age- and education-specific cutoff scores for dementia derived from this cohort [28]. For the CASI-short, we used a score ≤25 as the cutoff score for dementia. Computer algorithms were used to apply DSM-IV criteria for dementia to the questionnaires obtained from informants. Details about the application of the algorithms and the validity of these methods are published elsewhere [29].

Statistical Analyses

We restricted our analyses to the 424 women who had no dementia at baseline as ascertained by an in-person evaluation, and who had at least 1 additional follow-up evaluation. Hazard ratios (HRs) of incident dementia associated with estrogen-related variables as measured by the *Leisure World Cohort Study* were estimated using Cox regression analysis [30]. Age at study entry was the age at enrollment in *The 90+ Study* (delayed entry) and the event of interest was age at dementia diagnosis. HRs for each estrogen-related variable were adjusted

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for age using age (continuous) as the fundamental time scale and with and without the covariate of education (high school, vocational school or some college, college graduate). We also controlled for years of exogenous estrogen use in the EEEI analysis. Participants were followed until age of dementia diagnosis, death or last visit. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Separate analyses were performed for each estrogen-related factor and the EEEI and no adjustment in the p-values was made for multiple comparisons.

Results

For the 424 participants the mean (standard deviation) was 68.5 (5.0) for age at enrollment in the *Leisure World Cohort Study*, 93.2 (2.6), for age at enrollment in *The 90+ Study*, 96.5 (3.2) for age at last follow-up, 3.4 (2.5) for years of follow-up. Dementia was diagnosed in 209 (49%) at a mean age of 96.5 (3.1).

No menstrual / reproductive variable (Table 1) was associated with risk of dementia after age 90. Adjustment for education had essentially no effect on the observed HRs. Women with a late age (30+) at first child or who had no child tended to have reduced dementia risk (HR= 0.69, 95% CI 0.42–1.13). However, the result was not statistically significant.

EEEI ranged from 10.6 to 48.4, mean=33.9, standard deviation=4.3 and was marginally associated with risk of incident dementia (HR=0.99, 95% CI 0.95–1.02). Women with a high EEEI (≥ 35.9) had a non-significant reduced risk (HR=0.75, 95% CI 0.53–1.06) relative to women with EEEI < 32.7) (Table 1). Adjustment for education had little effect on the HR. Nor did years of exogenous estrogen use; for women with a high EEEI the adjusted HR was 0.74, (95% CI 0.52–1.04).

Neither dose, duration, type nor time since last use of estrogen replacement was associated with risk of dementia after age 90 with or without adjustment for education (Table 2).

Discussion

We found little evidence to support the theory that exposure to endogenous or exogenous estrogen influences dementia risk in late life. We analyzed separately the factors commonly recognized as relative to estrogen and found none to be related to risk. This extends the lack of association of endogenous exposure and dementia risk to the oldest-old group (90+ years).

We also calculated an EEEI to include markers up to the time of menopause with clear effects on estrogen levels. We had no information on breast feeding and therefore could not include its effect in the index. It is difficult to know the relative weights to give to different periods of estrogen exposure, but the proposed EEEI provides a shorthand description of several key estrogen exposure periods and warrants further study. The only finding approaching significance in the current study was a reduced risk with high EEEI.

Exogenous estrogen exposure in this cohort was limited to menopausal estrogen use. We had no information on use of oral contraceptives (OC). OC were first approved by the FDA in

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1960. At that time, our youngest participant was aged 57 and OC use, if any, was likely to be minimal.

Strengths of this study are its longitudinal design, dementia diagnosis procedures, complete follow-up, and estrogen variables accessed 25 years earlier (nearer to the time of the events and long before potential cognitive dysfunction might affect recall); limitations include its small size. With a larger size, the observed trend of increased risk of dementia with high endogenous estrogen exposure would be more precise. Additionally, as reproductive history and post-menopausal estrogen use likely effect mortality, selective removal of those at risk of developing dementia may occur. Our results are also limited to dementia risk in the oldest-old (those who survive to age 90).

Although estrogens exert potentially neuroprotective effects on brain structure and function [31] and have been found to be related to better cognitive performance [12], its influence on dementia risk in this oldest-old cohort was marginal.

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Table 1.

Risk of incident dementia (2003–2019) by menstrual and reproductive data collected in the 1980s.

			Hazard Ratio (95% CI)	
	No dementia (n=215)	**Dementia (n=209)**	**Univariate**	**Adjusted for education**
Age at menarche				
≤ 12	78 (36%)	67 (32%)	1.00	1.00
13	62 (29%)	68 (33%)	1.22 (0.87–1.72)	1.22 (0.87–1.72)
14+	75 (35%)	74 (35%)	0.86 (0.61–1.20)	0.85 (0.61–1.19)
Number of children (5 missing)				
0	66 (31%)	52 (25%)	1.00	1.00
1	28 (13%)	34 (16%)	0.99 (0.64–1.53)	0.98 (0.64–1.52)
2	76 (36%)	76 (37%)	1.23 (0.86–1.75)	1.23 (0.86–1.75)
3+	42 (20%)	45 (22%)	1.14 (0.76–1.70)	1.18 (0.79–1.76)
Age at first child (9 missing)				
≤ 20	11 (5%)	20 (10%)	1.00	1.00
21–24	46 (22%)	40 (20%)	0.85 (0.49–1.45)	0.88 (0.51–1.51)
25–29	55 (26%)	65 (32%)	0.99 (0.60–1.64)	1.06 (0.63–1.77)
30+	34 (16%)	26 (13%)	0.58 (0.32–1.05)	0.63 (0.35–1.15)
No child	66 (31%)	52 (26%)	0.75 (0.45–1.27)	0.79 (0.47–1.34)
Menopause (2 missing)				
Natural	139 (65%)	132 (63%)	1.00	1.00
Surgical without bilateral oophorectomy	33 (15%)	35 (17%)	1.28 (0.88–1.86)	1.24 (0.85–1.81)
Bilateral oophorectomy	29 (14%)	28 (13%)	1.17 (0.78–1.76)	1.14 (0.75–1.72)
Surgical NOS	12 (6%)	14 (7%)	0.97 (0.56–1.69)	0.94 (0.54–1.63)
Menopause (2 missing)				
Natural	139 (65%)	132 (63%)	1.00	1.00
Surgical	74 (35%)	77 (37%)	1.17 (0.88–1.55)	1.14 (0.85–1.51)
Age at last menstrual period (4 missing)				
≤ 44	56 (26%)	43 (21%)	1.00	1.00
45–54	125 (59%)	137 (66%)	1.19 (0.84–1.68)	1.19 (0.84–1.68)
55+	31 (15%)	28 (13%)	1.09 (0.67–1.76)	1.13 (0.70–1.82)
Reproductive years (4 missing)				
≤ 32	67 (32%)	63 (30%)	1.00	1.00
33–38	69 (33%)	81 (39%)	1.06 (0.76–1.48)	1.06 (0.76–1.47)
39+	76 (36%)	64 (31%)	0.84 (0.59–1.19)	0.84 (0.59–1.20)
Endogenous estrogen exposure index (13 missing)				
≤ 32.6	63 (30%)	71 (35%)	1.00	1.00
32.7–35.8	72 (34%)	70 (35%)	0.96 (0.69–1.33)	0.95 (0.68–1.33)
35.9+	74 (35%)	61 (30%)	0.75 (0.53–1.06)	0.77 (0.54–1.08)

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Table 2.

Risk of incident dementia (2003–2019) by use of estrogen replacement therapy data collected in the 1980s.

			Hazard Ratio (95% CI)*	
	No dementia (n=215)	**Dementia (n=209)**	**Univariate**	**Adjusted for education**
Estrogen replacement therapy (ERT)				
Never	68 (32%)	59 (28%)	1.00	1.00
Ever	147 (68%)	150 (72%)	0.96 (0.71–1.30)	0.94 (0.69–1.28)
ERT duration in years (2 missing)				
≤ 3	39 (18%)	49 (23%)	1.02 (0.70–1.49)	1.04 (0.71–1.53)
4–14	50 (23%)	62 (30%)	1.27 (0.89–1.83)	1.32 (0.92–1.91)
15+	56 (26%)	39 (19%)	0.84 (0.56–1.27)	0.85 (0.57–1.28)
ERT years since last use (2 missing)				
15+	19 (9%)	33 (16%)	1.04 (0.68–1.59)	1.06 (0.69–1.64)
2–14	66 (31%)	67 (32%)	1.10 (0.77–1.56)	1.13 (0.79–1.61)
0–1	60 (28%)	50 (24%)	0.99 (0.68–1.45)	1.00 (0.68–1.46)
ERT dose of Premarin® in mg (76 other estrogen)				
≤ 0.62	52 (29%)	54 (32%)	1.05 (0.72–1.53)	1.07 (0.73–1.55)
≥ 1.25	60 (33%)	55 (33%)	0.95 (0.66–1.38)	0.95 (0.66–1.38)
Estrogen type				
Oral estrogen only	90 (42%)	94 (45%)	1.00 (0.72–1.38)	1.02 (0.73–1.42)
Oral and other estrogen	45 (21%)	46 (22%)	1.17 (0.79–1.73)	1.18 (0.80–1.75)
Injection and cream	12 (6%)	10 (5%)	0.99 (0.51–1.95)	0.99 (0.51–1.95)

*All hazard ratios are relative to category “Never estrogen”