ORIGINAL CONTRIBUTION

# Postmenopausal Estrogen Use Affects Risk for Parkinson Disease

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**Background:** Although estrogen therapy has been associated with improved cognitive functioning, a reduced risk of dementia in women with Parkinson disease (PD), and a decreased risk of Alzheimer disease, estrogen therapy has not affected the risk of PD per se.

**Objective:** To determine whether postmenopausal women with PD differed from control subjects with regard to estrogen exposure.

**Design, Setting, and Patients:** A case-control design was used, abstracting questionnaire data obtained via interview from 133 female PD cases and 128 female controls during routine outpatient clinic visits in 1999 at a mid-Atlantic tertiary care referral center. There were 140 subjects (68 PD cases and 72 controls) who met the inclusion criteria.

**Main Outcome Measure:** Use of postmenopausal estrogen therapy.

**Results:** More women in the control group than in the PD group took postmenopausal estrogen (36 [50%] of 72 women vs 17 [25%] of 68 women; $P<.003$), and women who had taken postmenopausal estrogen were less likely to develop PD than those who had not (odds ratio, 0.40 [95% confidence interval, 0.19-0.84]; $P<.02$). Among PD cases only, postmenopausal estrogen use was not associated with age of onset.

**Conclusion:** Postmenopausal estrogen therapy may be associated with a reduced risk of PD in women.

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THE ROLE OF ESTROGEN therapy (ET) in Parkinson disease (PD) symptoms and pathogenesis is controversial.[1] Some studies[2-4] suggest estrogen use is associated with improved motor functioning, whereas others have concluded that estrogen increases disease severity[5-7] and is correlated with an earlier age of onset.[3] Still other studies[8,9] have found no relationship between estrogen and PD symptoms. Although ET has been associated with improved cognitive functioning,[2] a reduced risk of dementia in women with PD,[10] and a decreased risk of Alzheimer disease,[11-13] ET has not affected the risk of PD per se.[10,14-16]

## METHODS

### SUBJECTS

Subjects were recruited from the Movement Disorders Clinic at the University of Virginia in 1999. Cases were included if they met the criteria for idiopathic parkinsonism, which included 2 of the 3 cardinal features of PD and no atypical features. Control subjects were either spouses of men with PD or friends of female PD cases who accompanied them to the clinic appointment. Subjects with cognitive impairment were not approached to participate in the study. Informed consent was obtained from each subject at the clinic visit before administration of the interview questionnaire. Subjects were told of the general nature of the study, but no information was given regarding the specific research questions or hypotheses of the study. By using a semistructured questionnaire, we interviewed 133 consecutive female PD cases and 128 consecutive female controls regarding their menstrual history, use of birth control pills (BCPs), parity, type of menopause, and use and duration of postmenopausal ET. Age at menopause was determined by asking subjects the date that they stopped having regular periods.

Data from cases and controls were used for analysis if subjects met the following inclusion criteria: no menstruation for at least 12 continuous months; menopause due to natural causes (ie, no procedures that would have caused cessation of menses); and for PD cases, initiation of ET before disease onset. There were no restrictions imposed on control subjects regarding the initiation of ET. We restricted our inclusion of subjects to those with no menses for at least 1 year to increase the likelihood of sampling only menopausal women, and we did not include women whose menopause was due to hysterectomy to maximize the homogeneity of our sample. Of the 261 women inter-

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viewed, we excluded 121 for the following reasons: 10 PD cases and 14 controls were actively menstruating, 39 cases and 42 controls were experiencing menopause due to hysterectomy, and 16 cases started ET after their PD onset.

### DATA ANALYSIS

Data from the 140 subjects (68 PD cases and 72 controls) meeting our inclusion criteria were analyzed using *t* tests for continuous variables and $\chi^2$ tests for categorical variables. Data from subjects whose duration of BCP use and/or ET use was less than 1 year were coded as "never used."

Conditional logistic regression models were used to investigate the independent effect of a risk or protective factor after adjustment for one or several other factors and to adjust for confounding variables (eg, age). Crude and adjusted odds ratios were used to estimate the relative risk of PD. All probability (*P*) values are 2-tailed.

## RESULTS

At the interview, the mean±SD age of the PD cases and controls was 71±8 and 66±8 years, respectively ($P<.001$). Among PD cases, the age of PD onset ranged from 33 to 80 years, with a mean±SD of 63±10 years, and the disease duration ranged from less than 1 to 29 years, with a mean±SD of 8±6 years. The **Table** shows the summary statistics, group proportions, and results of comparisons between cases and controls regarding menstrual history, use of BCPs, and use of ET. In the control group, 50% of the women used postmenopausal ET compared with 25% of the women with PD. In addition, there was a trend for more women in the control group to have taken BCPs, although this difference did not achieve statistical significance. There were no significant differences between the groups for age at menarche, age at menopause, menses duration, parity, BCP duration, age at starting postmenopausal ET, or duration of ET.

We examined the association between estrogen exposure and PD, controlling for differences in the ages between PD cases and controls, by conditional logistic regression analysis. Postmenopausal ET was associated with a lower risk of PD (crude odds ratio, 0.33 [95% confidence interval, 0.16-0.68]; $P<.003$) (adjusted odds ratio, 0.40 [95% confidence interval, 0.19-0.84]; $P<.02$).

Among PD cases only, there was no difference in the mean±SD age of PD onset between women who took postmenopausal ET (n=17, 64±9 years) and those who did not (n=51, 63±10 years) ($P<.99$).

**Estrogen Exposure of PD Case and Control Subjects**

| Variable | Cases (n = 68) | Controls (n = 72) | *P* Value |
|---|---|---|---|
| Age, y | | | |
| At menarche | | | |
| Range | 9-17 | 9-16 | <.19 |
| Mean ± SD | 13 ± 2 | 13 ± 1 | |
| At menopause | | | |
| Range | 31-60 | 38-63 | <.21 |
| Mean ± SD | 49 ± 6 | 50 ± 5 | |
| Menses duration, y | | | |
| Range | 18-48 | 24-52 | <.12 |
| Mean ± SD | 36 ± 6 | 37 ± 5 | |
| No. of pregnancies | | | |
| Range | 0-9 | 0-9 | <.39 |
| Mean ± SD | 3 ± 2 | 3 ± 2 | |
| BCP use, No. (%) | 13 (19) | 24 (33) | <.08 |
| BCP duration, y | | | |
| Range | 1-30 | 1-28 | <.69 |
| Mean ± SD | 8 ± 9 | 7 ± 7 | |
| ET use, No. (%) | 17 (25) | 36 (50) | <.003 |
| Age ET was started, y | | | |
| Range | 40-79 | 21-76 | <.93 |
| Mean ± SD | 54 ± 12 | 54 ± 11 | |
| ET duration, y | | | |
| Range | 1-30 | 1-28 | <.31 |
| Mean ± SD | 12 ± 8 | 9 ± 9 | |

Abbreviations: BCP, birth control pill; ET, estrogen therapy; PD, Parkinson disease.

## COMMENT

Our finding that more women without PD used postmenopausal estrogen compared with women with PD is similar to that reported previously.[17] However, our finding that ET use was a significant factor in reducing the risk of PD contradicts the results of other studies[8,9] in which estrogen had neither beneficial nor deleterious effects. In our study, women who did not take postmenopausal estrogen had a 2½ times greater risk of having PD than women who used ET.

We did not find evidence of a relationship between ET and age of PD onset, which has been reported by others.[3] Whether the difference in age between cases and controls explains the lack of evidence of such a relationship should be considered. The control subjects' significantly younger age at enrollment may have led to sampling errors related to social, cultural, and/or educational differences that influenced their decision to use postmenopausal estrogen; no information related to such factors was collected in this study. In addition, if postmenopausal estrogen indeed decreases parkinsonian symptoms, as has been suggested by some,[2-4] then it is possible that subjects in our control group may actually be undiagnosed PD cases with minimal disease symptoms. However, given that the mean±SD age of PD onset in our cohort of PD cases is 63±10 years, our control subjects' mean and median age of 66 years indicates that they have achieved a substantial portion of their age of PD risk.

Our findings that postmenopausal ET was associated with a lower risk of PD and a trend for more women in the control group to have taken BCPs may provide support for the notion of an interaction effect between estrogen and other endogenous and/or exogenous factors, which has been suggested by other studies.[9,14-16] Several potential interactions between estrogen and other endogenous or exogenous factors with regard to PD risk have been described. Strijks et al[9] reported that while estrogen had no effect on PD patients' motor functioning, the use of progesterone worsened the symptoms of parkinsonism. An increased risk of PD among women with a history of hysterectomy and postmenopausal estrogen use was reported by Popat et al,[15] and the PD risk increased with duration of estrogen exposure. Shulman et al[16] found that weight and body mass index were significantly lower among men and

women with PD compared with controls. These researchers concluded that, because corticosteroid precursors are converted to estrogen by adipose tissue, PD cases' lower weight and body mass may interfere with endogenous estrogen production and, thus, inhibit its neuroprotective potential. Ascherio et al[14] reported that caffeine reduces the risk of PD among women who do not use postmenopausal hormones, but increases risk among hormone users. In addition, cigarette smoking also seemed to modify the association between use of hormones and risk of PD; unlike in our study, use of oral contraceptives for 5 or more years was actually correlated with PD. Thus, numerous types of potential interactions between estrogen and other factors have been suggested.

The strengths of the present study were its use of data obtained from women whose menopause was due to natural causes only and its exclusion of subjects who had undergone surgical hysterectomies. Our study also had several limitations. First, because of the small sample size, the study had limited power to test the association between estrogen use and PD. Second, our findings could be biased because of the study's reliance on subjects' recall of their menstrual history and estrogen use. In addition, selection bias may be present because we did not collect information on subjects' educational or socioeconomic level and, therefore, we were unable to explore whether these factors were correlated with ET use. Third, the lack of data in our study regarding BCP and ET preparations used (eg, progesterone and progestin additives) may confound our findings because differences in exogenous estrogen exposure could not be examined. On the other hand, interview questions regarding BCP and ET preparations might have increased our risk of recall bias. Finally, our results may be biased by our exclusion of PD cases who began ET after disease onset. Such censoring of cases without equivalent censoring of controls may have created an artifact in our results.

The issues surrounding use of ET by postmenopausal women are becoming increasingly important due to the conflicting evidence about its beneficial effect in preventing cardiovascular disease, osteoporosis, and dementia. Although a recent study[11] reported that ET for 1 year did not slow disease progression in women with mild to moderate Alzheimer disease, women with low levels of endogenous estradiol were 4 to 6 times as likely to have AD compared with women with higher estradiol levels.[18] Other studies[11-13] also have found an association between ET use and decreased risk of Alzheimer disease. These findings may be more relevant to a therapeutic role for ET in preventing dementia within the setting of PD than the use of estrogen as prophylaxis for PD per se.

Our findings and those of Benedetti et al[17] are sufficiently suggestive to support the conclusion that further research is needed in which sufficiently large and homogeneous samples of female cases and controls are used. In addition, future research needs to use multifactorial designs in which endogenous, exogenous, genetic, and environmental variables are included because of the possibility of interaction effects. Detailed information regarding drug name and dosage of oral contraceptives and ETs would allow analytic consideration of subjects' exposure to the numerous and varying formulations. Moreover, the collection of data pertaining to body weight, nicotine exposure, and caffeine exposure would allow multivariate analyses to be conducted. Such research may not only elucidate more clearly the role of estrogen as neuroprotective and factors associated with the risk of PD but may also clarify the seemingly contradictory findings reported across studies.

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