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Lifetime exposure to estrogens and Parkinson's disease in California teachers

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ABSTRACT

Introduction: Parkinson's disease (PD) is consistently observed to occur less frequently in women than men, prompting investigation into whether estrogen protects against neurodegeneration of dopaminergic neurons.
Methods: We used baseline data in the California Teachers Study, a prospective cohort of women, to investigate whether reproductive factors indicating higher long-term estrogen levels are associated with PD using a nested case-control approach. We identified 228 PD cases and 3349 unaffected controls frequency matched by age and race.
Results: Women who reported using combined estrogen/progesterone therapy or progesterone only formulations had a 57% increase in PD risk (OR = 1.57, 95% CI = 1.06, 2.34) compared to never having used HT. Compared to women with menopause at 50–52 years, menopause at younger (<35–46 years: OR = 0.59, 95% CI = 0.37, 0.94) and older ages (≥53 years: OR = 0.54, 95% CI = 0.36, 0.83) had lower PD risk. A derived composite estrogen summary score for women's exposure to both endogenous and exogenous estrogens throughout life indicated that women with presumed higher cumulative lifetime levels of estrogen (a score of 3–5) had a significantly reduced PD risk [(OR = 0.57, 95% CI = 0.35, 0.91) relative to those with lower lifetime estrogen exposure or a composite estrogen summary score of 0–1].
Conclusions: These results provide some support for the hypothesis that lifelong high estrogen is protective in PD, suggesting that the level and persistence of exposure over the long term may be important in PD risk reduction.

1. Introduction

Parkinson's disease is consistently observed to occur less frequently in women than men at an approximate ratio of 1:1.5 [1]. This raises the question whether female hormones, specifically estrogens and progesterone, protect against neurodegeneration of dopaminergic neurons in the brain. Experimental studies in animals and cells suggest that estrogen might be neuroprotective through anti-oxidative, anti-inflammatory, and anti-apoptotic pathways, and provide some support for its role in upregulating neurotrophic factors [2]. Estrogen has been shown experimentally to increase brain dopamine concentrations and influence dopamine receptor density and sensitivity [3].

Epidemiologic studies examining hormonal factors in PD have reported somewhat inconsistent results, with few including prospectively collected data from population cohorts [4–12]. Some suggest that conditions resulting in a shorter lifespan of physiologic estrogen levels increase PD risk in women, while others report that treatment with estrogens decrease risk, and still others do not find any association between estrogens and PD. An increased PD risk was reported for post-menopausal hormone use in a case-control study among Kaiser Permanente members in Northern California [9] and in the Cancer Prevention cohort [4], but inverse associations were found in three case-control studies [5,6,10]. The Nurses'

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Health Study found progesterone only formulations as being associated with increases in PD risk [12]. Early age at menopause increased PD risk in two studies [5,10], but was protective in another [9]. Results for age at menarche [6,9,10,12], parity [4,6,9,10,12] and type of menopause [9,12] have generally been inconsistent or null. Conflicting findings leave unanswered questions about potential effects of reproductive hormones and the reproductive cycle on PD risk in women.

We used data from the California Teachers Study (CTS), a prospective cohort study of women that collected comprehensive data on reproductive and hormone-related factors to investigate associations in PD cases and controls using a nested case-control study design.

2. Materials and methods

2.1. Study population

The CTS is a cohort of female public school teachers and administrators that was established in 1995–1996 to study breast cancer and other women's health issues [13]. The CTS enrolled 133,479 active and retired female members of the State Teachers Retirement System (STRS) who completed a baseline questionnaire. The study protocol was approved by institutional review boards of participating institutions.

A third follow-up questionnaire administered to 72,266 active cohort members in 2005, included an item, "Were you ever told by a health professional that you have Parkinson's disease? At what age?". Of 69,527 respondents, 404 who answered "yes" were identified as potential PD cases. Using self-reported age at diagnosis, 58 (14%) were initially considered "prevalent cases" (diagnosed before study entry in 1995); 208 (51%) were "incident" cases (new diagnoses between study entry and third follow-up). 138 (34%) did not provide an age of onset ("unknown onset" cases).

2.2. Verification of Parkinson's diagnosis

In 2010–2011, we conducted a follow-back study to confirm PD diagnosis. Through National Death Index (NDI) records linkage matching, we identified 77 of 404 potential cases as deceased (44 incident, 22 prevalent, 11 unknown onset). CTS staff attempted to contact surviving cases (n = 327) by telephone or mail, and invited them to provide permission to contact their neurologists or primary care physicians.

We utilized public records searches to locate contact information if letters were undeliverable. After multiple unsuccessful attempts, cases who did not respond, refused, or could not be located were considered not reachable. Some cases who responded but reported that they did not have PD were also excluded.

Cases who agreed to participate received a medical records release form and HIPAA authorization. Physicians completed a diagnostic questionnaire reporting PD signs and symptoms and diagnosis ("definite", "probable", "uncertain" or "no PD"), or provided a copy of medical records, which we (YB) reviewed to verify diagnosis relying broadly on Gelb and UK Brain Bank criteria [14,15].

During the follow-back, we identified an additional 16 cases who were deceased (10 incident, 1 prevalent, 5 unknown onset). For the 93 total deceased, we attempted to and obtained 74 (80%) death certificates (DC). PD was listed on 35 (47%) as underlying or multiple cause of death (COD) (Fig. 1), and we considered this confirmatory of PD diagnosis. However, since PD frequently is not listed as a COD in patients with PD [16], we did not interpret the absence of PD on DC as refuting diagnosis except for the CODs listed as the following: Lewy Body disease, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), extrapyramidial diseases, dementias including Alzheimer's disease (AD) and multi-infarct dementia, which reflect conditions commonly misdiagnosed as PD [listed on 17 DCs (23%)]. None of these diagnoses or PD was found on 22 DCs (30%).

Of cases presumed to be alive, 77 of 152 incident and 19 of 35 prevalent cases were reached; 55 (71%) and 11 (60%) were diagnostically confirmed, respectively (Fig. 1). Cases for whom we were unable to establish contact or obtain a DC, we considered self-reported diagnosis valid. In total, 178 incident (86%), 50 prevalent (86%) and two unknown onset (1%) (re-classified as incident upon review of medical records) cases were validated as true possible or probable PD.

It became clear that unknown onset cases were largely response errors, since only 1% of those reached were diagnostically confirmed. These cases were on average 10 years younger than incident or prevalent cases at baseline, which corroborated suspicions that they were different than the confirmed incident and prevalent cases. Therefore, whenever unable to confirm PD diagnosis, we considered unknown onset cases invalid (Fig. 1).

2.3. Selection of controls

Controls (n = 3349) were selected randomly from respondents of the third follow-up questionnaire not answering "yes" to the PD question, using frequency matching (1:10 ratio) based on birth year (5-year categories) and race of cases.

2.4. Source of data

We used data reported on the baseline CTS questionnaire ten years prior to the third follow-up to examine reproductive factors influencing hormone levels: age at

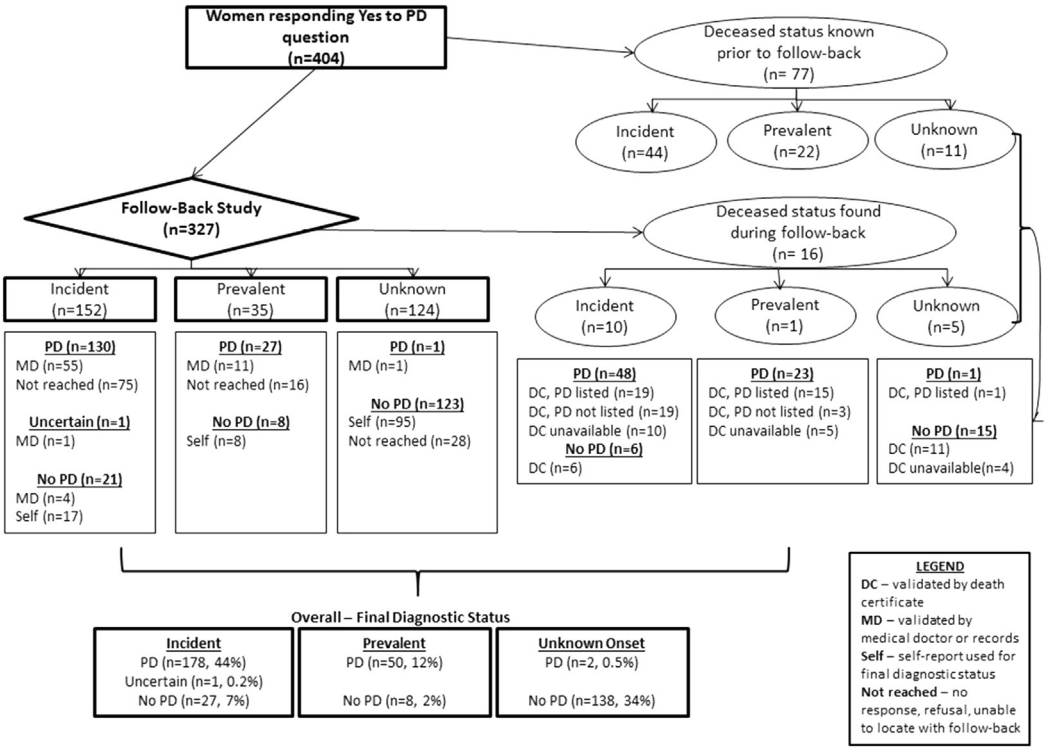

Fig. 1. Follow-back study of Parkinson's disease process and final disposition, California Teachers Study.