The Long-Term Effects of Oophorectomy on Cognitive and Motor Aging Are Age Dependent

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Key Words

Oophorectomy · Estrogen · Neuroprotection · Parkinson’s disease · Parkinsonism · Dementia · Cognitive impairment · Menopause

Abstract

Background: The evidence for a neuroprotective effect of estrogen in women remains controversial. Objective: We studied the long-term risk of parkinsonism and of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Methods: We conducted a historical cohort study among all women residing in Olmsted County, Minn., USA, who underwent unilateral or bilateral oophorectomy before the onset of menopause for a non-cancer indication from 1950 through 1987. Each member of the oophorectomy cohort was matched by age to a referent woman from the same population who had not undergone oophorectomy. In total, we studied 1,252 women with unilateral oophorectomy, 1,075 women with bilateral oophorectomy, and 2,368 referent women. Women were followed for a median of 25–30 years. Parkinsonism was assessed using screening and examination, through a medical records-linkage system, and through death certificates. Cognitive status was assessed using a structured questionnaire via a direct or proxy telephone interview. Results: The risk of parkinsonism and of cognitive impairment or dementia increased following oophorectomy. In particular, we observed significant linear trends of increasing risk for either outcome with younger age at oophorectomy. Conclusion: Our findings, combined with previous laboratory and epidemiologic findings, suggest that estrogen may have an age-dependent neuroprotective effect.

Introduction

We previously reported from the Mayo Clinic Cohort Study of Oophorectomy and Aging that bilateral oophorectomy performed before age 45 years is associated with increased overall mortality, as well as mortality caused by neurological and psychiatric disorders [1]. In addition, we reported that women who underwent either unilateral or bilateral oophorectomy have an increased risk of parkinsonism and of cognitive impairment or dementia [2, 3]. In this paper, we provide additional evidence that the effect of oophorectomy on the brain may be age dependent.

Participants and Methods

Study Sample

The Mayo Clinic Cohort Study of Oophorectomy and Aging included women who underwent unilateral or bilateral oophorectomy and a group of women who did not undergo oophorectomy.
Epidemiology Project

dents provided by the records-linkage system of the Rochester
tomy and 1,097 who underwent bilateral oophorectomy (fig. 1 ).
for the study 1,293 women who underwent unilateral oophorec-
death shortly after the surgery. Therefore, we considered eligible
lignancy (usually breast cancer) because they were at high risk of
ovarian cancer or as treatment for another estrogen-related ma-
( or before age 56 years if age at menopause was unknown). In ad-
2002), and had their oophorectomy before the onset of menopause
born before 1962 ( i.e., were at least 40 years old by January 1,
the original cohort were included in the current study if they were
from the medical records by trained study nurses. Women from
fined by the gynecologist at the time of surgery was abstracted
with census enumerations.

Potential referent women were identified from a list of resi-
dents provided by the records-linkage system of the Rochester
Epidemiology Project [5]. This listing has been shown to be com-
plete compared with a random digit dialing telephone sample and
with census enumerations [5]. For each woman in the oophorec-
tomy cohort, we defined the year of the surgical procedure as the
index year (n = 2,390; fig. 1 ). All women in the population who
met these criteria were considered eligible regardless of any pos-
sible diseases or risk factors (population-based referent sample).

Follow-Up Procedures

Women in the oophorectomy and referent cohorts were con-
tacted once during the follow-up study spanning from 2001
through 2006. All women underwent the same procedures to as-
ss the incidence of parkinsonism and of cognitive impairment
or dementia following the index year. Parkinsonism was assessed
through a two-phase survey with individual telephone screening
of the women (or their proxy) for parkinsonism and examination
of those who screened positive (when alive), as described in detail
elsewhere [2]. In addition, independent of the screening, all wom-
en were also followed passively for parkinsonism (but not for cog-
nitive impairment or dementia) through review of medical re-
cords in the records-linkage system of the Rochester Epidemiol-
ogy Project and through death certificates ( if deceased ) [2].
Cognitive impairment or dementia were assessed using the Tele-
phone Interview for Cognitive Status-modified (12 items; maxi-
mum score = 50 points) or through a brief dementia questionnaire
administered to a proxy informant (8 questions), as described in
detail elsewhere [3].

All telephone contacts were made by one of 6 specifically
trained research assistants and were direct whenever possible; for
deceased or otherwise incapacitated women ( e.g., deaf, cognitively
impaired, or terminally ill), we contacted the best available
proxy ( most knowledgeable person in the family ) [2, 3]. All tele-
phone interviewers and all research team members involved in the
ascertainment of the outcome conditions were kept unin-
formed of the oophorectomy or referent status of women to pre-
vent bias.

<table>
<thead>
<tr>
<th>Oophorectomy cohort</th>
<th>Referent cohort</th>
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<tbody>
<tr>
<td>Unilateral = 1,293</td>
<td>Total = 2,390</td>
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<tr>
<td>Bilateral = 1,097</td>
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<tr>
<td>Total = 2,390</td>
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<th>Follow-up study 2001–2006</th>
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<tr>
<td>Followed for:</td>
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<tr>
<td>Parkinsonism = 2,368</td>
</tr>
<tr>
<td>Dementia = 1,472</td>
</tr>
<tr>
<td>Alive = 1,699*</td>
</tr>
<tr>
<td>Deceased = 574*</td>
</tr>
</tbody>
</table>

| Total = 2,390 |

Fig. 1. Overall design of the Mayo Clinic Cohort Study of Oophorectomy and Aging. The numbers of women included in the follow-up were different for parkinsonism and for cognitive impairment or dementia. The numbers for cognitive impairment or dementia were reduced because only the women who were interviewed were informative. The asterisk indicates that a total of 95 referent women underwent oophorectomy after the index year and from 1950 through 1987. Because these women were included in both cohorts, they were counted only in the oophorectomy cohort regarding vital status at follow-up (2001–2006).
Statistical Analyses

Women were censored at the end of the study (spanning from 2001 through 2006), at death, or at last contact. We estimated the hazard ratio (HR) using Cox proportional hazards models. The assumption of proportional hazards was assessed by graphical methods and by introducing a time-dependent coefficient in the Cox models [6]. The analyses presented here were stratified by age at surgery (in tertiles). In the analyses for cognitive impairment or dementia, we included only 813 women with unilateral oophorectomy, 676 women with bilateral oophorectomy, and 1,472 referent women because the assessment was limited to telephone interviews (no passive follow-up through medical records or death certificates) [3]. All analyses were conducted using SAS version 8.2, and statistical tests were performed at the two-tailed alpha level of 0.05.

Results

Figure 1 shows the overall design of the study. The number of women included in the follow-up was different for Parkinsonism and for cognitive impairment or dementia. The assessment of Parkinsonism included both active contacts and passive information. By contrast, the assessment of cognitive impairment or dementia included only direct or proxy interviews. The median follow-up was long (median = 25–30 years). Figure 2 shows the trend of increasing HRs for Parkinsonism in women with younger age at oophorectomy (either unilateral or bilateral). A test for linear trend in the log HRs was significant (p = 0.01). Figure 3 shows the trend of increasing HRs for cognitive impairment or dementia in women with younger age at oophorectomy (either unilateral or bilateral). A test for linear trend in the log HRs was significant (p < 0.0001).

Discussion and Conclusions

This study showed an increased long-term risk of Parkinsonism and of cognitive impairment or dementia in women who underwent oophorectomy before menopause. The magnitude of the association increased with younger age at oophorectomy. Findings from this study, combined with findings from studies in laboratory animals [7, 8] and from other epidemiologic studies [9–11], suggest that the estrogen deficiency caused by bilateral oophorectomy was the initial step in a chain of causality that determined the increased risk of neurological diseases. The increased risk among women who underwent unilateral oophorectomy may be explained by the premature failure of the contralateral ovary caused by the oophorectomy itself or by the concurrent hysterectomy (70.1% of all unilateral oophorectomies). However, the effect of oophorectomy on the brain may be mediated by other mechanisms such as a deficiency of progesterone or testosterone or by the disruption of the hypothalamic-pituitary-gonadal axis. Finally, one or several susceptibility genes may be involved in causing the association. Further discussion of these biological mechanisms was provided elsewhere [2, 3].
Our findings for parkinsonism and for cognitive impairment or dementia in aggregate suggest that the putative neuroprotective effect of estrogen may be general and may involve multiple mechanisms and multiple neuronal populations. In addition, our findings suggest that the putative neuroprotective effect of estrogen may be age dependent and that there may be a critical age window for neuroprotection. The concept of a critical age window for neuroprotection has been proposed by several other investigators [7–11].

Acknowledgments

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References