Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause

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ABSTRACT

Objective: There is increasing laboratory evidence for a neuroprotective effect of estrogen; however, the clinical and epidemiologic evidence remains limited and conflicting. We studied the association of oophorectomy performed before the onset of menopause with the risk of subsequent cognitive impairment or dementia.

Methods: We included all women who underwent unilateral or bilateral oophorectomy before the onset of menopause for a non-cancer indication while residing in Olmsted County, MN, 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 813 women with unilateral oophorectomy, 676 women with bilateral oophorectomy, and 1,472 referent women. Women were followed through death or end of study using either direct or proxy interviews.

Results: Women who underwent either unilateral or bilateral oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared to referent women (hazard ratio [HR] = 1.46; 95% CI 1.13 to 1.90; adjusted for education, type of interview, and history of depression). The risk increased with younger age at oophorectomy (test for linear trend; adjusted $p < 0.0001$). These associations were similar regardless of the indication for the oophorectomy, and for women who underwent unilateral or bilateral oophorectomy considered separately.

Conclusions: Both unilateral and bilateral oophorectomy preceding the onset of menopause are associated with an increased risk of cognitive impairment or dementia. The effect is age-dependent and suggests a critical age window for neuroprotection. *Neurology*® 2007;69:1074–1083

GLOSSARY

AD = Alzheimer disease; **ADL** = activities of daily living; **HR** = hazard ratio; **TICS-m** = Telephone Interview for Cognitive Status-modified; **WHI** = Women's Health Initiative.

An association between estrogen and cognitive impairment or dementia is biologically plausible, and several mechanisms of action have been postulated in laboratory research: 1) estrogen improves synapse formation on dendritic spines in hippocampi of oophorectomized rats[1,2]; 2) estrogen may improve cerebral blood flow and glucose metabolism, and it may act as an antioxidant[1-3]; 3) estrogen increases choline acetyltransferase activity in the basal forebrains and hippocampi of oophorectomized rats[3,4]; 4) estrogen reduces the deposition of β-amyloid in the brain, whereas progesterone has the opposite effect[5,6]; 5) estrogen prevents β-amyloid 1-42 from inducing a rise in intracellular calcium and from causing mitochondrial damage.[7,8] In addition, three meta-analyses showed a 20% to

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40% reduction in risk of Alzheimer disease (AD) for women who used estrogen treatment after menopause.[9-11]

These laboratory and clinical findings are in apparent conflict with findings from the Women's Health Initiative (WHI) clinical trials that showed an increased rather than a decreased risk of dementia or mild cognitive impairment in women treated by either estrogen alone or estrogen plus progestin at age 65 years or later.[12-15] However, these conflicting findings may be explained by an age-dependent effect of estrogen on the brain as hypothesized by several investigators.[8,16-19] In particular, estrogen may have a protective effect on the brain if given to women who underwent oophorectomy before reaching natural menopause or if given in the perimenopausal and early postmenopausal years to women with natural menopause. By contrast, estrogen may have deleterious effects on the brain if started many years after the onset of natural menopause. Therefore, there may be a critical age window for neuroprotection.[20] The same age-dependent effect of estrogen was observed for overall mortality[21] and for cardiovascular diseases.[22] Thus, we studied the risk of cognitive impairment or dementia in a population-based sample of women with and without oophorectomy who were enrolled in the Mayo Clinic Cohort Study of Oophorectomy and Aging.[21]

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 (referent cohort). Both groups were followed using the same methods. All study procedures were approved by the institutional review boards of the Mayo Clinic and of Olmsted Medical Center. All women who were examined as part of the study signed an informed consent form.[21]

During the 38-year period from 1950 through 1987, 1,433 women residing in Olmsted County, MN, had a unilateral oophorectomy, and 1,824 underwent a bilateral oophorectomy (including 110 who had a second unilateral oophorectomy). Oophorectomy was defined as complete removal of the ovary. Further details about the oophorectomy cohort were reported elsewhere.[21,23] The indication for oophorectomy as defined by the gynecologist at the time of surgery was abstracted from the medical records by trained study nurses. Women from the original cohort were included in the current study if they were born before 1962 (i.e., were at least 40 years old by January 1, 2002), and had their oophorectomy before the onset of menopause (or before age 56 years if age at menopause was unknown). In addition, we excluded women who underwent oophorectomy for ovarian cancer or as treatment for another estrogen-related malignancy (usually breast cancer) because they were at high risk of death shortly after the surgery.

Potential referent women were identified from a list of residents provided by the records-linkage system of the Rochester Epidemiology Project.[24] This list has been shown to be complete by comparison with a random digit dialing telephone sample and with census enumerations.[24] For each woman in the oophorectomy cohort, we defined the year of the surgical procedure as the index year, and we selected (via simple random sampling) one woman from the complete Olmsted County population with the same year of birth, who had survived without oophorectomy to the index year. All women in the population who met these criteria were considered eligible irrespective of any possible diseases or risk factors (population-based referent sample).

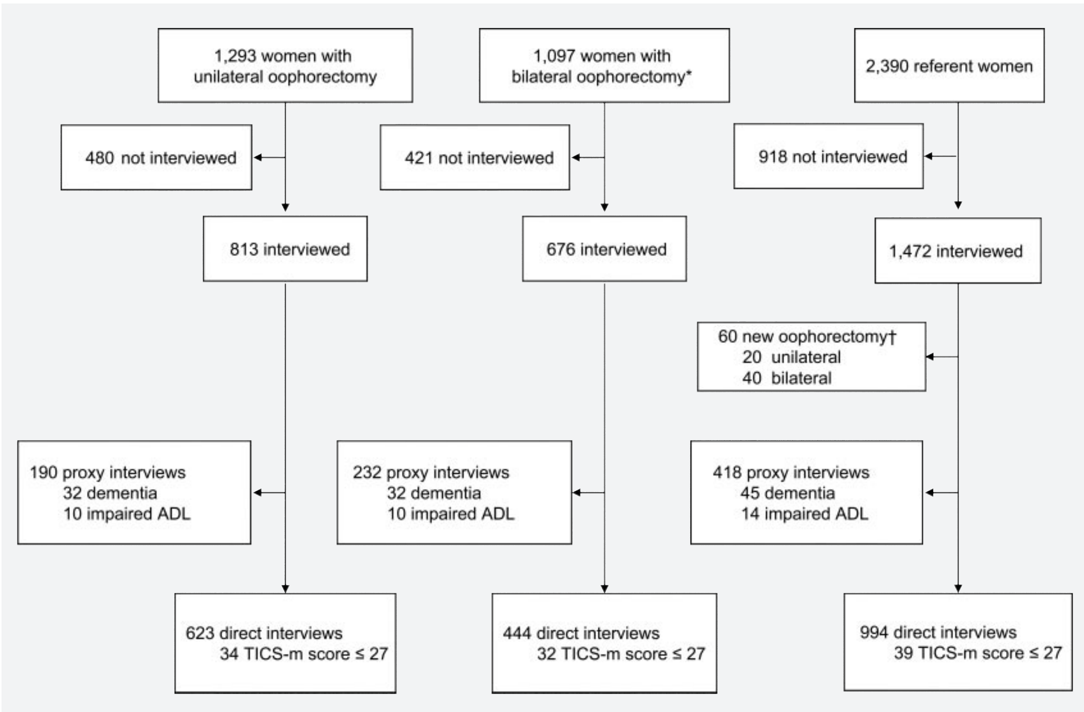
Follow-up procedures. Both cohorts were followed via telephone interview by one of six trained research assistants who were kept uninformed of the oophorectomy or referent status of the women. We administered the Telephone Interview for Cognitive Status-modified (TICS-m; 12 items; maximum score = 50 points) to all living women who could be interviewed.[25-27] Women who died before the study or were incapacitated (e.g., deaf, cognitively impaired, or terminally ill) were assessed by interviewing a proxy informant and using a brief dementia questionnaire (eight questions). We initially identified a contact person from the records-linkage system or from other sources and asked him or her to judge who would be the most knowledgeable proxy. The best proxy was then invited to serve as the informant.

The dementia questionnaire included five questions about memory impairment (remembering things like a short shopping list, things to do, or events that happened recently; finding her way, even in familiar places; recognizing family members; remembering the exact day or year; problems with her memory), one question about impaired activities of daily living caused by cognitive problems ("Does/Did she need help to dress, eat, or bathe because of confusion, poor judgment, or other thinking problems?"), one question about prior diagnosis of dementia or senility, and one question about prior diagnosis of AD. These eight questions were derived from an existing more detailed dementia questionnaire, but were modified and adapted for our study.[28] The direct and proxy interviews were mutually exclusive.

Women were considered affected by cognitive impairment or dementia if they met one of the following three criteria: 1) they scored ≤27 on the TICS-m at direct interview; 2) a proxy respondent reported a previous diagnosis of dementia, senility, or AD; 3) a proxy respondent reported impairment in activities of daily living (dressing, eating, or bathing) caused by cognitive problems. Consistent with these three criteria, age at onset was defined as the age at administration of the TICS-m (direct contact only), age at onset of dementia reported by a proxy, or age at onset of impairment in activities of daily living reported by a proxy. Whenever the proxy was unable to report an age at onset of cognitive decline or dementia, we used either age at death or age at the time of interview (carry forward imputation).

Validity. We investigated the validity of the brief dementia questionnaire using data from a previous study conducted in

Figure 1 Flowchart of study cohorts



*Menopause due to the oophorectomy in 843 women; oophorectomy within 2 years after menopause in 96 women (arbitrary cut-off chosen to include the perimenopausal period); and age at menopause unknown in 158 women, but oophorectomy done before age 56 years. †A total of 57 women were included in the referent cohort before oophorectomy and in the respective oophorectomy subcohort after the surgery. An additional three women underwent bilateral oophorectomy for a cancer indication and were censored at the time of oophorectomy. ADL = activities of daily living; TICS-m = Telephone Interview for Cognitive Status-modified.

the same Olmsted County population.[29] As part of that study, we were able to compare 265 proxy administrations of the dementia questionnaire via telephone with the independent documentation of dementia in medical records of the records-linkage system. Medical records were considered an adequate standard for comparison only when the person had been in contact with the system within 3 years of the time of interview or within 3 years of death. The brief dementia questionnaire had 73.3% sensitivity and 85.6% specificity for AD and 44.6% sensitivity and 92.2% specificity for all types of dementia. The sensitivity for all types of dementia was increased somewhat by also including women for whom the proxy informant reported a positive response to three or more out of five memory questions (sensitivity = 48.7%).

In addition, for 845 women assessed via proxy in this study, we studied the internal consistency of the brief dementia questionnaire. The agreement between the two questions about prior diagnoses and the question about impaired activities of daily living was 89.8% (kappa = 0.51; 95% CI 0.42 to 0.60). More importantly, the agreement was similar for women with oophorectomy and for referent women ($p = 0.84$).

The TICS-m was previously validated by others,[25,30,31] and the cut-off score of ≤27 was previously established.[30,31] In addition, we studied the convergent validity of the TICS-m with the Mini-Mental State Examination in a sample of 397 individuals with both measures (Spearman's correlation = 0.48; $p < 0.0001$).[32]

Statistical analysis. Women were censored at the end of the study (staggered over 2001 through 2006) or at death. Those who could not be followed via telephone interview were excluded. We obtained cumulative incidence curves using the Kaplan-Meier method and estimated the hazard ratio (HR) using Cox proportional hazards models. Because these models allowed for complete age adjustment by using age as the time scale, all estimates of HRs used the full cohort of referent women for comparison to increase statistical power. The assumption of proportional hazards was assessed by graphical methods and by introducing a time-dependent coefficient in the Cox models. For each analysis, we obtained unadjusted HRs and HRs adjusted by education (four classes: <9; 9 to 12; 13 to 16; >16 years of school),[33] history of depression at index year (ever vs never), and type of interview (direct vs proxy) to prevent possible confounding effects.

Analyses were conducted overall for any oophorectomy, for the unilateral and bilateral oophorectomy subcohorts separately, and in strata defined by surgical indication and by age at surgery (in tertiles). Because the age at surgery was younger for women who underwent unilateral oophorectomy compared with women who underwent bilateral oophorectomy, the tertile cut-offs were different for the two subcohorts. In addition, because the majority of women who underwent bilateral oophorectomy were prescribed estrogen treatment, we also conducted analyses stratified by age at the start of estrogen deficiency (age at end of estrogen treatment after the oophorectomy; in tertiles). Information about estrogen treatment was abstracted from the inpatient and out-

Table 1 Documentation of the diagnosis of cognitive impairment or dementia among women who underwent oophorectomy and among referent women in Olmsted County, MN

Cohort	Women with cognitive impairment or dementia	Direct interview, TICS-m, n (%)	Proxy interview: Dementia, senility, or AD, n (%)	Proxy interview: Impairment in ADL, n (%)
Any oophorectomy	150	66 (44.0)	64 (42.7)	20 (13.3)
Unilateral oophorectomy	76	34 (44.7)	32 (42.1)	10 (13.2)
Bilateral oophorectomy	74	32 (43.2)	32 (43.2)	10 (13.5)
Referent women	98	39 (39.8)	45 (45.9)	14 (14.3)
Total	248	105 (42.3)	109 (44.0)	34 (13.7)

TICS-m = Telephone Interview for Cognitive Status-modified; AD = Alzheimer disease; ADL = activities of daily living.

patient medical records in the records-linkage system.[24] All analyses were done using SAS version 8.2, and statistical tests were performed at the two-tailed alpha level of 0.05.

RESULTS Figure 1 shows detailed flowcharts for the three subcohorts. We recruited 1,293 women with unilateral oophorectomy but were unable to interview 480 of them. Among the remaining 813 (62.9%) women included in the study, 602 (74.0%) oophorectomies were performed because of a benign ovarian condition (cyst 196; endometriosis 128; benign tumor 105; inflammation 68; other rare conditions 105), whereas 211 (26.0%) oophorectomies had no specified indication (no recognized benign ovarian condition). A total of 541 (66.5%) oophorectomies were in conjunction with hysterectomy, and 28 (3.4%) women had undergone hysterectomy prior to the removal of the ovary. Altogether, these women were followed for a median of 29.2 years (range = 63 days to 53.8 years). A total of 623 (76.6%) women were interviewed directly (alive); 178 (21.9%) were interviewed via proxy because they had died; and 12 (1.5%) were interviewed via proxy but were still alive (total proxy interviews = 190). A total of 76 women developed cognitive impairment or dementia (table 1).

We recruited 1,097 women with bilateral oophorectomy but were unable to interview 421 of them. Among the remaining 676 (61.6%) women included in the study, 339 (50.1%) oophorectomies were performed because of a benign ovarian condition (cyst 86; endometriosis 138; benign tumor 48; inflammation 31; other rare conditions 36), whereas 337 (49.9%) oophorectomies were prophylactic. A total of 637 (94.2%) oophorectomies were in conjunction with hysterectomy, and 22 (3.3%) women had undergone hysterectomy prior to the removal of their ovaries. Altogether, these women were followed for a median of 25.1 years (range = 4 days to 53.8 years). A total of 444 (65.7%) women were interviewed directly; 226 (33.4%) were interviewed via proxy because they had died; and 6 (0.9%) were interviewed via proxy but were still alive (total proxy interviews = 232). A total of 74 women in this group developed cognitive impairment or dementia (table 1).

Finally, we recruited 2,390 referent women who did not undergo an oophorectomy through the index year. We were unable to interview 918 of them. Of the remaining 1,472 (61.6%) women included in the study, 60 had a subsequent oophorectomy from 1950 through 1987. Fifty-seven of these 60 women were included in the referent cohort before oophorectomy and in the respective oophorectomy subcohort after the surgery. The remaining three referent women underwent bilateral oophorectomy for a cancer indication and were included only in the referent cohort (censored at the time of oophorectomy). Altogether, referent women were followed for a median of 26.5 years (range = 165 days to 53.6 years). A total of 994 (70.4%) women were interviewed directly; 398 (28.2%) were interviewed via proxy because they had died; and 20 (1.4%) were interviewed via proxy but were still alive (total proxy interviews = 418). A total of 98 women developed cognitive impairment or dementia (table 1).

Table 2 shows analyses combining women who had either unilateral or bilateral oophorectomy compared with the referent cohort. Overall, women who underwent any oophorectomy experienced an increased risk of cognitive impairment or dementia compared to referent women (figure 2). In strata by age, there was a trend of increasing risk with younger age at the time of surgery (test for linear trend in the adjusted log HR; $p < 0.0001$). The indication for surgery did not modify the association.

Table 3 shows analyses comparing women who had unilateral oophorectomy with the referent cohort. Overall, we observed an increased risk

Table 2 Cohort analyses for women who underwent either unilateral or bilateral oophorectomy and for referent women in Olmsted County, MN

Cohort or stratum	Women at risk	Follow-up (person-years)	Women with cognitive impairment or dementia	Unadjusted hazard ratio (95% CI)*	p	Adjusted hazard ratio (95% CI)†	p
Overall							
Referent women	1,472	39,044	98	1.0 (ref.)	—	1.0 (ref.)	—
Any oophorectomy	1,489	40,736	150	1.45 (1.12–1.87)	0.005	1.46 (1.13–1.90)	0.005
Age at surgery, y‡							
T1 (<38)	529	15,713	28	2.79 (1.81–4.31)	<0.0001	2.89 (1.86–4.48)	<0.0001
T2 (38–45)	432	11,909	43	1.57 (1.09–2.25)	0.01	1.54 (1.06–2.23)	0.02
T3 (>45)	528	13,114	79	1.19 (0.88–1.61)	0.25	1.22 (0.90–1.65)	0.21
T1 + T2 (≤45)	961	27,622	71	1.88 (1.38–2.56)	<0.0001	1.88 (1.37–2.58)	0.0001
Indication for surgery§							
Benign conditions	941	26,867	86	1.47 (1.10–1.97)	0.009	1.46 (1.08–1.96)	0.01
No specified indication¶	548	13,869	64	1.42 (1.03–1.94)	0.03	1.47 (1.06–2.02)	0.02
Analyses including a broader definition of cognitive impairment‖							
Referent women	1,472	38,916	117	1.0 (ref.)	—	1.0 (ref.)	—
Any oophorectomy	1,489	40,606	167	1.35 (1.06–1.71)	0.01	1.34 (1.05–1.71)	0.02

*Hazard ratios estimated using Cox regression models not including possible confounding variables. These estimates are adjusted only by age (used as the time scale).

†Hazard ratios estimated using Cox regression models including education (<9; 9–12; 13–16; >16 years), history of depression (ever vs never), and type of interview (direct vs proxy). These analyses excluded the 52 women (29 referent and 23 oophorectomy) for whom years of education was unknown. Overall analyses stratified by education yielded an HR = 1.60 (95% CI 1.13 to 2.25) for ≤12 years of education and 1.32 (95% CI 0.88 to 1.99) for >12 years of education (difference $p = 0.49$).

‡T1, T2, and T3 indicate the first, second, and third tertiles. A test for linear trend of the log HRs was significant (unadjusted $p < 0.0001$; adjusted $p < 0.0001$).

§A formal test for interaction was not significant (unadjusted $p = 0.82$; adjusted $p = 0.97$).

¶Prophylactic bilateral oophorectomy or unilateral oophorectomy with no specified indication and performed in the course of other surgery (usually hysterectomy).

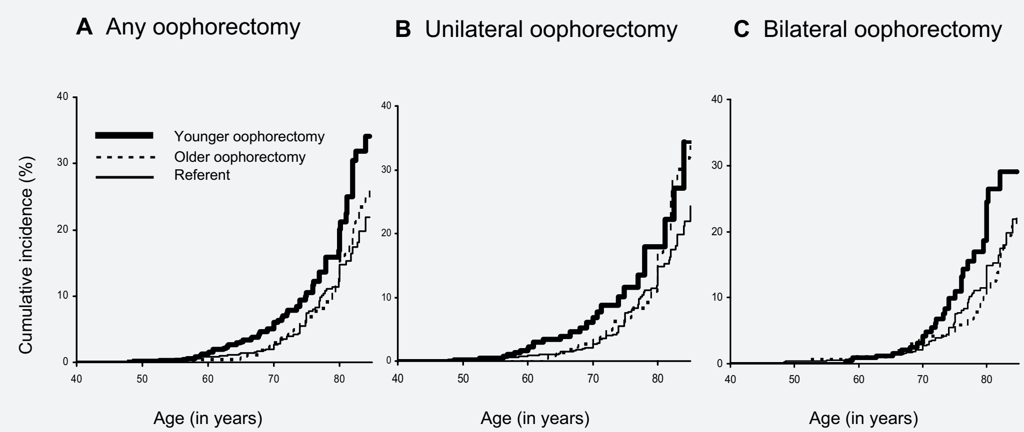
‖Adding those women for whom the proxy respondent reported three or more out of five memory questions.

of cognitive impairment or dementia (figure 2). In strata by age, there was a trend of increasing risk with younger age at the time of surgery (test for linear trend in the adjusted log HR; $p < 0.0001$). Neither the indication for the surgery nor concurrent hysterectomy modified the association.

Table 4 shows analyses comparing women who had bilateral oophorectomy with the referent cohort. Overall, the risk of cognitive impairment or dementia was not significantly increased (figure 2); however, it was significantly increased for oophorectomies performed before age 49 years (combined first and second tertiles), and there was a trend of increasing risk with younger age at the time of the surgery (test for linear trend in the adjusted log HR; $p = 0.01$). Interestingly, the increased risk was restricted to the stratum of women who underwent oophorectomy before age 49 years and were not given estrogen until at least age 50 years (the approximate median age at natural menopause). Similarly, analyses by age at estrogen deficiency (i.e., age at end of estrogen treatment after the oophorectomy, if any) showed a trend of increasing risk with younger age (test for linear trend in the adjusted log HR; $p = 0.01$). The indication for the surgery did not modify the association.

To investigate the possible bias caused by a selective nonparticipation in the follow-up, we compared the distribution of baseline characteristics in women included (interviewed) and excluded from the analyses (not interviewed). In the unilateral oophorectomy cohort, women interviewed and women not interviewed had similar distributions by age at surgery and indication, but not by concurrent hysterectomy (70.0% vs 64.6%; $p = 0.04$). In the bilateral oophorectomy cohort, women interviewed and women not interviewed had similar distributions by age at time of surgery, indication, and concurrent hysterectomy, but not by estrogen treatment for at least 6 months (53.1% vs 45.6%; $p = 0.02$). In the referent cohort, the distribution by age at index year was similar in women who were and were not interviewed.

Figure 2 Cumulative incidence of cognitive impairment or dementia in women with any oophorectomy (A), unilateral oophorectomy (B), and bilateral oophorectomy (C) compared with referent women



Women at risk

	A 40	A 50	A 60	A 70	A 80	B 40	B 50	B 60	B 70	B 80	C 40	C 50	C 60	C 70	C 80
Younger ooph.	636	869	619	290	78	497	463	295	115	22	139	405	333	168	42
Older ooph.	---	328	500	337	148	---	236	260	185	86	---	93	231	159	76
Referent	631	1,167	1,056	596	207	631	1,167	1,056	596	207	631	1,167	1,056	596	207

Younger oophorectomy = first and second tertiles combined (age ≤45 years for any oophorectomy, age ≤41 years for unilateral oophorectomy, and age ≤48 years for bilateral oophorectomy). Older oophorectomy = third tertile.

DISCUSSION This study showed an increased risk of cognitive impairment or dementia for women who underwent either unilateral or bilateral oophorectomy before the onset of menopause, or for those who underwent unilateral oophorectomy considered separately. The findings for bilateral oophorectomy considered separately were significant only when the oophorectomy was done before age 49 years. For both unilateral and bilateral oophorectomy, the association was age-dependent, and the risk increased with younger age at surgery.

In this same cohort study, women who underwent prophylactic bilateral oophorectomy before age 45 years experienced an increased mortality for all causes and, in particular, for neurologic and mental disorders, as reported elsewhere.[21] Those findings suggest that our HRs for cognitive impairment or dementia may be underestimated if the women who died were at increased risk of dementia (selective censoring). However, sensitivity analyses removing the 12 women who died within 1 year of the oophorectomy or of the index year yielded consistent findings (data not shown).

We suggest three possible mechanisms to explain the observed associations. These mechanisms are not mutually exclusive and may play different roles within individuals and across individuals. First, our findings may suggest that oophorectomy-induced estrogen deficiency was the initial step in a chain of causality that determined the increased risk of cognitive impairment or dementia. In support of a neuroprotective effect of estrogen, women who underwent bilateral oophorectomy before age 49 years but were given estrogen treatment until at least age 50 years had no increased risk. In addition, the risk of cognitive impairment or dementia did not vary with the indication for the bilateral oophorectomy. Unfortunately, our study did not address the possible biologic mechanisms linking estrogen deficiency with risk of dementia. In particular, it remains uncertain whether the brain lesions underlying dementia were of vascular nature, of degenerative nature, or a combination of both. Nevertheless, our findings for cognitive impairment or dementia, combined with our findings for parkinsonism reported elsewhere,[34] suggest that the neuroprotective effect of estrogen may be general and may involve multiple mechanisms and multiple neuronal populations.

The increased risk of cognitive impairment or dementia among women who underwent unilateral oophorectomy may be explained by the premature estrogen deficiency caused by the concurrent hysterectomy (70.0% of all unilateral oophorectomies). Hysterectomy may compromise the blood supply to the remaining ovary, leading to premature ovarian failure.[35-37] We further explored this hypothesis using data from this study. In a random sample of 436 women (approximately 10% of all women included in our original cohort), we collected extensive information on estrogen treatment, and we found a significantly earlier age at initiation of estrogen treatment in the perimenopausal period for

Table 3 Cohort analyses for women who underwent unilateral oophorectomy and for referent women in Olmsted County, MN

Cohort or stratum	Women at risk	Follow-up (person-years)	Women with cognitive impairment or dementia	Unadjusted hazard ratio (95% CI)*	p	Adjusted hazard ratio (95% CI)†	p
Overall							
Referent women	1,472	39,044	98	1.0 (ref.)	—	1.0 (ref.)	—
Unilateral oophorectomy	813	23,751	76	1.63 (1.20–2.20)	0.002	1.64 (1.20–2.23)	0.002
Age at surgery, y‡							
T1 (< 34)	291	8,889	14	4.03 (2.23–7.29)	<0.0001	4.61 (2.52–8.43)	<0.0001
T2 (34–41)	243	6,979	13	1.27 (0.71–2.28)	0.42	1.23 (0.67–2.26)	0.51
T3 (> 41)	279	7,883	49	1.49 (1.05–2.10)	0.02	1.50 (1.05–2.13)	0.03
T1 + T2 (≤ 41)	534	15,868	27	1.93 (1.25–2.99)	0.003	1.98 (1.26–3.11)	0.003
With hysterectomy§	326	9,308	18	1.79 (1.07–2.99)	0.03	1.83 (1.07–3.11)	0.03
Without hysterectomy	208	6,560	9	1.88 (0.94–3.76)	0.08	1.85 (0.92–3.72)	0.09
Indication for surgery¶							
Benign conditions	602	17,938	51	1.50 (1.06–2.10)	0.02	1.44 (1.02–2.05)	0.04
No specified indication‖	211	5,813	25	1.97 (1.27–3.06)	0.003	2.24 (1.43–3.50)	0.0004
Concurrent hysterectomy**							
With hysterectomy	569	16,128	61	1.64 (1.19–2.26)	0.003	1.62 (1.16–2.25)	0.005
Without hysterectomy	244	7,624	15	1.57 (0.91–2.71)	0.11	1.74 (1.00–3.02)	0.049
Analyses including a broader definition of cognitive impairment††							
Referent women	1,472	38,916	117	1.0 (ref.)	—	1.0 (ref.)	—
Any oophorectomy	813	23,691	84	1.48 (1.12–1.97)	0.006	1.48 (1.11–1.98)	0.008

*Hazard ratios estimated using Cox regression models not including possible confounding variables. These estimates are adjusted only by age (used as the time scale).
†Hazard ratios estimated using Cox regression models including education (<9; 9–12; 13–16; >16 years), history of depression (ever vs never), and type of interview (direct vs proxy). These analyses excluded the 38 women (29 referent and 9 unilateral oophorectomy) for whom years of education was unknown. Overall analyses stratified by education yielded an HR = 1.84 (95% CI 1.23 to 2.74) for ≤12 years of education and 1.42 (95% CI 0.87 to 2.32) for >12 years of education (difference $p = 0.36$).
‡T1, T2, and T3 indicate the first, second, and third tertiles. A test for linear trend of the log HRs was significant (unadjusted $p < 0.0001$; adjusted $p < 0.0001$).
§A formal test for interaction was not significant (unadjusted $p = 0.91$; adjusted $p = 0.97$). Hysterectomy was performed either concurrently or preceding the oophorectomy.
¶A formal test of interaction was not significant (unadjusted $p = 0.26$; adjusted $p = 0.08$).
‖Unilateral oophorectomy with no specified indication and performed in the course of other surgery (usually hysterectomy).
**A formal test for interaction was not significant (unadjusted $p = 0.88$; adjusted $p = 0.80$). Hysterectomy was performed either concurrently with or preceding the oophorectomy.
††Adding those women for whom the proxy respondent reported three or more out of five memory questions.

women who underwent unilateral oophorectomy with or without hysterectomy (median = 46.9 years) than for referent women (median = 50.8 years; $p = 0.02$). These findings support the hypothesis that unilateral oophorectomy or the concurrent hysterectomy may contribute to premature ovarian failure, leading to premature menopausal symptoms, in turn leading to an earlier initiation of estrogen treatment.

Second, the association between oophorectomy and increased risk of cognitive impairment or dementia may be explained completely or in part by a deficit in progesterone and testosterone rather than in estrogen secreted by the ovaries. However, the effect of progesterone and testosterone on cognition in women remains uncertain.[13,38,39] Third, the association between oophorectomy and increased risk of cognitive impairment or dementia may be due to one or several susceptibility genes that increase the risk of both outcomes independently (i.e., confounding by genetic predisposition). Genetic variants may determine ovarian diseases prompting the oophorectomy, or they may cause uterine diseases or symptoms that prompt hysterectomy, in turn, prompting oophorectomy.[40,41] These same genetic variants may independently increase the risk of subsequent cognitive impairment or dementia. However, our analyses stratified by indication for the oophorectomy did not reveal any significant interactions.

Table 4 Cohort analyses for women who underwent bilateral oophorectomy and for referent women in Olmsted County, MN

Cohort or stratum	Women at risk	Follow-up (person-years)	Women with cognitive impairment or dementia	Unadjusted hazard ratio (95% CI)*	p	Adjusted hazard ratio (95% CI)†	p
Overall							
Referent women	1,472	39,044	98	1.0 (ref.)	—	1.0 (ref.)	—
Bilateral oophorectomy	676	16,985	74	1.31 (0.96–1.77)	0.09	1.33 (0.98–1.81)	0.07
Age at surgery, y‡							
T1 (<43)	224	6,109	13	1.67 (0.93–3.00)	0.08	1.74 (0.97–3.14)	0.06
T2 (43–48)	203	5,060	23	1.60 (1.01–2.52)	0.04	1.68 (1.06–2.66)	0.03
T3 (>48)	249	5,816	38	1.10 (0.75–1.60)	0.63	1.09 (0.74–1.61)	0.66
T1 + T2 (≤48)	427	11,169	36	1.62 (1.10–2.39)	0.01	1.70 (1.15–2.51)	0.008
Estrogen given to age 50 y	87	2,285	3	0.67 (0.21–2.14)	0.50	0.79 (0.25–2.54)	0.69
Estrogen not given to age 50 y	340	8,884	33	1.86 (1.25–2.77)	0.002	1.89 (1.27–2.83)	0.002
Age at estrogen deficiency, y§							
T1 (<46)	210	5,807	22	1.79 (1.13–2.85)	0.01	1.82 (1.14–2.91)	0.01
T2 (46–51)	211	5,055	22	1.27 (0.80–2.02)	0.31	1.32 (0.82–2.10)	0.25
T3 (> 51)	255	6,122	30	1.11 (0.73–1.67)	0.63	1.11 (0.73–1.69)	0.63
T1 + T2 (≤ 51)	421	10,862	44	1.49 (1.04–2.13)	0.03	1.53 (1.07–2.19)	0.02
Indication for surgery¶							
Benign conditions	339	8,929	35	1.43 (0.97–2.11)	0.07	1.50 (1.01–2.21)	0.04
Prophylactic‖	337	8,056	39	1.21 (0.83–1.76)	0.32	1.21 (0.83–1.77)	0.33
Analyses including a broader definition of cognitive impairment**							
Referent women	1,472	38,916	117	1.0 (ref.)	—	1.0 (ref.)	—
Any oophorectomy	676	16,915	83	1.24 (0.93–1.64)	0.15	1.24 (0.93–1.65)	0.15

*Hazard ratios estimated using Cox regression models not including possible confounding variables. These estimates are adjusted only by age (used as the time scale).

†Hazard ratios estimated using Cox regression models including education (<9; 9–12; 13–16; >16 years), history of depression (ever vs never), and type of interview (direct vs proxy). These analyses excluded the 43 women (29 referent and 14 bilateral oophorectomy) for whom years of education was unknown. Overall analyses stratified by education yielded an HR = 1.45 (95% CI 0.97 to 2.17) for ≤12 years of education and 1.27 (95% CI 0.78 to 2.05) for >12 years of education (difference $p = 0.78$).

‡T1, T2, and T3 indicate the first, second, and third tertiles. A test for linear trend of the log HRs was significant (unadjusted $p = 0.02$; adjusted $p = 0.01$).

§Age at estrogen deficiency = age at oophorectomy plus total duration of subsequent estrogen treatment. A test for linear trend of the HRs was significant (unadjusted $p = 0.02$; adjusted $p = 0.01$).

¶A formal test of interaction was not significant (unadjusted $p = 0.47$; adjusted $p = 0.37$).

‖Prophylactic in the course of other surgery (usually hysterectomy).

**Adding those women for whom the proxy respondent reported three or more out of five memory questions.

This study has several strengths. In particular, the two oophorectomy subcohorts and the referent cohort were representative of the general population, and the follow-up was long (median = 25 to 30 years). On the other hand, this study has some limitations, and not all potential biases could be controlled. Because of funding restrictions, the documentation of cognitive impairment or dementia was limited to telephone information, and only 62% of all women in the three subcohorts participated. However, participants and nonparticipants were similar regarding age at baseline in the unilateral, bilateral, and referent subcohorts, and regarding indication for the surgery in the unilateral and bilateral subcohorts.

Second, the direct or proxy telephone assessments of cognitive impairment or dementia were imperfect. However, in addition to the published validity data for the TICS-m,[25,30,31] we reported a good convergent validity between the TICS-m and the Mini-Mental State Examination from our own experience.[32] The eight questions in the brief dementia questionnaire were derived from an existing instrument,[28] had face validity, and were simple. In addition, we reported adequate validity data from our own experience. Similar brief dementia questionnaires were introduced and validated by other investigators.[42,43] Finally, sensitivity analyses using a broader definition of cognitive impairment or dementia, and analyses adjusted by type of interview, yielded consistent results.

Third, for some women who were interviewed via proxy, we imputed the missing age at onset of cognitive impairment or dementia. However, sensitivity analyses excluding the five women with unknown age at onset yielded consistent findings (data not shown). Fourth, the oophorectomies took place over 38 years, from 1950 through 1987, when surgical practice and estrogen use may have differed from current standards. However, our analyses stratified by index year showed no differences between 1950 to 1969 and 1970 to 1987 (data not shown). Fifth, some of the stratified analyses were based on small numbers. Therefore, they had limited power and some risk of false-positive findings because of multiple testing.

Despite some methodologic limitations that could not be addressed with the resources available, this study is one of the first to support the hypothesis of a critical age window for the protective effect of estrogen on the brain in humans.[20] These findings also have important clinical implications and should prompt a reassessment of prophylactic oophorectomy in premenopausal women and of the use of estrogen treatment following oophorectomy.[21,44-46]

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NOTE ADDED IN PROOF

The verbatim text of the brief dementia questionnaire is now available elsewhere (Rocca WA, Bower JH, Ahlskog JE, et al. Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. Arch Neurol, in press).

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