

Hysterectomy, Oophorectomy, Estrogen, and the Risk of Dementia

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Key Words

Hysterectomy · Oophorectomy · Menopause · Estrogen · Neuroprotection · Dementia · Cognitive impairment

Abstract

Background: The long-term cognitive effects of hysterectomy and oophorectomy remain controversial. **Objective:** To explore the association of hysterectomy and oophorectomy with the subsequent risk of cognitive impairment or dementia. **Methods:** We combined the results from two cohort studies graphically and conducted additional analyses. **Results:** Combined results from the Mayo Clinic Cohort Study of Oophorectomy and Aging and from a Danish nationwide cohort study suggest that the extent of gynecologic surgery may correlate with a stepwise increase in the risk of cognitive impairment or dementia. Compared with women with no gynecologic surgeries, the risk of cognitive impairment or dementia was increased in women who had hysterectomy alone, further increased in women who had hysterectomy with unilateral oophorectomy, and further increased in women who had hysterectomy with bilateral oophorectomy. The risk increased with younger age at the time

of the surgery. **Conclusion:** We hypothesize that both hysterectomy and oophorectomy may have harmful brain effects via direct endocrinological mechanisms or other more complex mechanisms. Estrogen deficiency appears to play a key role in these associations, and estrogen therapy may partly offset the negative effects of the surgeries.

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Introduction

In the Mayo Clinic Cohort Study of Oophorectomy and Aging (MCSO), we observed an increased risk of cognitive impairment or dementia in women who underwent either unilateral or bilateral oophorectomy before the onset of natural menopause [1]. These findings have been confirmed and extended by a Danish nationwide study to include hysterectomy [2]. This article combines the findings from the MCSO and the Danish study to develop a new hypothesis on the long-term effect of hysterectomy and oophorectomy on cognitive aging. Additional studies on this topic were reviewed elsewhere [3].

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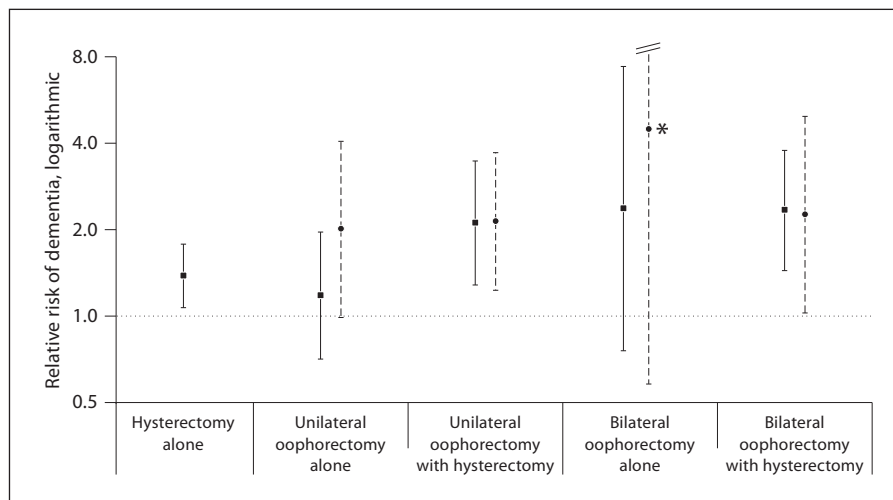
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Fig. 1. Relative risks or hazard ratios for cognitive impairment or dementia associated with hysterectomy, unilateral oophorectomy, and bilateral oophorectomy in the Danish nationwide study (squares and solid lines), and in the MCSO (circles and dotted lines) [1, 2]. The estimates for the MCSO were recomputed considering only oophorectomy before age 40 years for consistency with the Danish study. The asterisk indicates that the estimate was based on only 4 women, and the upper confidence limit of 33.8 is not shown.



Comparison of the Two Cohort Studies

The MCSO and the Danish study have some important methodological differences that make the comparison and combination of findings somewhat problematic. First, the emphasis of the Danish study was on hysterectomy whereas the emphasis of the MCSO was on oophorectomy. Thus, hysterectomy without oophorectomy was not included in the MCSO. Second, the significant findings in the Danish study were restricted to early-onset dementia assessed via a national registry. By contrast, in the MCSO, the outcome was cognitive impairment or dementia at all ages and measured via a direct or proxy interview [1, 2]. Third, because of the difference in the timing of the outcome, there was also a difference in the timing of the surgeries. Therefore, we reanalyzed the data in the MCSO considering only oophorectomy before age 40 years.

The Mayo Clinic Cohort Study of Oophorectomy and Aging

In the MCSO, we observed an increased risk of cognitive impairment or dementia in women who underwent bilateral oophorectomy before the onset of natural menopause (70% increased risk for oophorectomy before age 49 years). The risk increased with younger age at the time of oophorectomy, was independent of surgical indication, and was partly offset by estrogen therapy after oophorectomy [1]. Adjustment by level of education and history of depression in women, or by type of interview used to as-

sess cognitive impairment or dementia in the study did not affect the findings. Interestingly, 97% of women with bilateral oophorectomies had concurrent or preceding hysterectomy.

Unexpectedly, the MCSO also showed an increased risk of cognitive impairment or dementia in women who underwent unilateral oophorectomy. The risk was higher when the oophorectomy was performed before age 42 years (first and second tertiles) and was independent of surgical indication. Women who underwent unilateral oophorectomy without hysterectomy before age 42 years had approximately the same increased risk (85%) as women who underwent unilateral oophorectomy with hysterectomy before age 42 years (83%) [1]. However, the majority of unilateral oophorectomies in the MCSO were performed in conjunction with hysterectomy (70%). Figure 1 summarizes the results from the MCSO for unilateral and bilateral oophorectomy performed before age 40 years and compares them with the Danish results. Figure 2 shows the trend of increasing risk of cognitive impairment or dementia with younger age at the time of surgery (middle and lower blocks). This age trend is consistent with the timing hypothesis for the protective effects of estrogen on the brain [4, 5].

The Danish Nationwide Cohort Study

In 2010, the MCSO findings were confirmed and extended by the Danish nationwide historical cohort study to include women with hysterectomy [2]. In the Danish study, women who underwent hysterectomy with bilat-

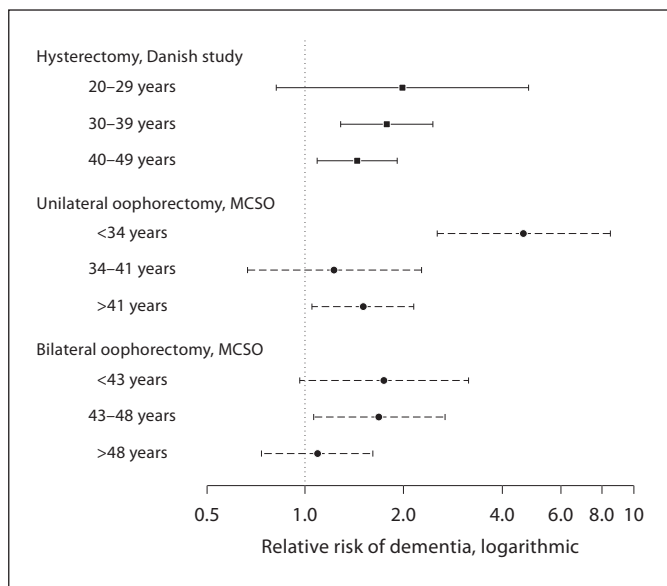


Fig. 2. Relative risks or hazard ratios for cognitive impairment or dementia associated with hysterectomy, unilateral oophorectomy, and bilateral oophorectomy stratified by age at the time of surgery in the Danish nationwide study (top block; squares and solid lines) and in the MCSO (middle and lower blocks; circles and dotted lines) [1, 2].

eral ovarian conservation had a 38% increase in risk of dementia with onset at ages 40–49 years. Hysterectomy with unilateral oophorectomy increased the risk by 110%, and hysterectomy with bilateral oophorectomy increased the risk by 133% [2]. Interestingly, women who underwent unilateral oophorectomy without concurrent hysterectomy did not have a statistically significant increased risk (18%), and women who underwent bilateral oophorectomy without hysterectomy had a nonsignificant 136% increased risk of early-onset dementia (fig. 1).

In stratified analyses, the risk of early-onset dementia increased with decreasing age at the time of hysterectomy (fig. 2, top block). Corresponding stratified analyses for unilateral or bilateral oophorectomy were not reported [2]. Analyses stratified by indication for surgery were not reported either.

Interpretation of Combined Findings

The MCSO and the Danish study are consistent in showing an increased risk of cognitive impairment or dementia in women who underwent either a unilateral or a bilateral oophorectomy (fig. 1). Surprisingly, in both

studies, the magnitude of the relative risk was similar for unilateral and bilateral oophorectomy, suggesting that there are important consequences of unilateral oophorectomy. In the Danish study, women who underwent bilateral oophorectomy with uterine conservation experienced an increased risk of early-onset dementia similar to women who had concurrent hysterectomy. By contrast, there were almost no women in the MCSO who underwent bilateral oophorectomy without a concurrent hysterectomy.

One area where the two studies differ is in unilateral oophorectomy without hysterectomy. In the Danish study, women with isolated unilateral oophorectomy had a nonsignificant increased risk of early-onset dementia (18% increase). By contrast, in the MCSO, women with unilateral oophorectomy experienced a similar increased risk of cognitive impairment or dementia regardless of concurrent hysterectomy (85 vs. 83% increase). This difference may reflect different surgical practices in the USA and Denmark [6]. For example, among 3,014 women who underwent any oophorectomy in Denmark, only 25% were unilateral [2]. By contrast, among 1,489 women with any oophorectomy included in the analyses for the MCSO, 55% were unilateral, and 70% of the unilateral oophorectomies were performed in conjunction with hysterectomy [1].

The findings from the MCSO and the Danish study can be combined to support an overall causal hypothesis. Bilateral oophorectomy causes an abrupt estrogen deficiency that may be the initial step in a chain of causality leading to increased risk of cognitive impairment or dementia. Other endocrinologic consequences of bilateral oophorectomy such as reduced levels of progesterone and testosterone or increased levels of gonadotropins may also be involved; however, estrogen seems to play a central role [4, 5]. Indeed, women in the MCSO who underwent bilateral oophorectomy before age 49 years but were treated with estrogen until at least age 50 years had no increased risk of cognitive impairment or dementia [1].

Hysterectomy alone may cause ovarian dysfunction via disturbances in blood flow to the ovaries or through other mechanisms [7, 8]. The ovarian dysfunction may in turn initiate the chain of causality mentioned above. The deleterious effects of hysterectomy appear to be stronger with younger age. The Danish study suggests that there are three steps of progressively increasing risk: (1) from referent women to hysterectomy; (2) next to hysterectomy plus unilateral oophorectomy, and (3) finally to hysterectomy plus bilateral oophorectomy (fig. 1). It remains uncertain how the removal of one ovary would influence the

function of the remaining contralateral ovary, especially when the uterus is not removed [7, 9].

The findings from the MCSO and the Danish study have major public health implications because as many as 25% of women in the USA and 10% of women in Denmark undergo hysterectomy, and a variable percent of these women undergo concurrent unilateral or bilateral oophorectomy [6]. If these associations are confirmed, they should prompt a more conservative approach to gynecologic surgery and a stronger recommendation for hormone therapy in women who undergo this surgery before the onset of natural menopause [4, 10].

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