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Increased Cardiovascular Mortality After Early Bilateral Oophorectomy

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Abstract and Introduction

Abstract

Objective: To investigate the mortality associated with cardiovascular diseases and the effect of estrogen treatment in women who underwent unilateral or bilateral oophorectomy before menopause.
Design: We conducted a cohort study with long-term follow-up of women in Olmsted County, MN, who underwent either unilateral or bilateral oophorectomy before the onset of menopause 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 any oophorectomy. We studied the mortality associated with cardiovascular disease in a total of 1,274 women with unilateral oophorectomy, 1,091 women with bilateral oophorectomy, and 2,383 referent women.
Results: Women who underwent unilateral oophorectomy experienced a reduced mortality associated with cardiovascular disease compared with referent women (hazard ratio [HR], 0.82; 95% CI, 0.67-0.99; *P* = 0.04). In contrast, women who underwent bilateral oophorectomy before age 45 years experienced an increased mortality associated with cardiovascular disease compared with referent women (HR, 1.44; 95% CI, 1.01-2.05; *P* = 0.04). Within this age stratum, the HR for mortality was significantly increased in women who were not treated with estrogen through age 45 years or longer (HR, 1.84; 95% CI, 1.27-2.68; *P* = 0.001) but not in women treated with estrogen (HR, 0.65; 95% CI, 0.30-1.41; *P* = 0.28; test of interaction, *P* = 0.01). Mortality was further increased after deaths associated with cerebrovascular causes were excluded.
Conclusions: Bilateral oophorectomy performed before age 45 years is associated with increased cardiovascular mortality, especially with cardiac mortality. However, estrogen treatment may reduce this risk.

Introduction

Every year, approximately 300,000 US women face the decision to undergo bilateral oophorectomy for the prevention of ovarian cancer.[1] For women who do not have genetic variants that increase the risk of ovarian cancer,[2,3] the risk-benefit balance of this preventive surgery remains uncertain and controversial.[1,4-6] Approximately 300,000 additional US women undergo bilateral oophorectomy for a benign condition every year.[7,8] For all of these combined 600,000 women, it remains uncertain whether estrogen treatment should be initiated after the surgery and for how many years it should be continued.[6,9-14]

To address the long-term health consequences of unilateral or bilateral oophorectomy and subsequent estrogen treatment in young women, we studied all cardiovascular conditions reported anywhere on the death certificates for 4,748 women included in the Mayo Clinic Cohort Study of Oophorectomy and Aging.[8,15-18]

Methods

Unilateral and Bilateral Oophorectomy Cohorts

The Mayo Clinic Cohort Study of Oophorectomy and Aging included a total of 1,274 women who underwent unilateral oophorectomy and 1,091 women who underwent bilateral oophorectomy from Olmsted County, MN, during the 38-year period from 1950 through 1987.[8] Oophorectomy was defined as complete removal of the ovary, and further details about the oophorectomy cohorts have been reported elsewhere.[7,19-21] All information about oophorectomy, including the indication defined by the gynecologist at the time of surgery, was abstracted from medical records included in the records-linkage system of the Rochester Epidemiology Project.[22] Women were included in the current study if they were born before 1962 (at least age 40 by January 1, 2002). In addition, we included only women who had undergone oophorectomy before menopause; however, we

also included 158 women with unknown age at menopause who underwent bilateral oophorectomy before age 56 years (approximate upper limit of age at natural menopause). Finally, we excluded women who underwent either unilateral or bilateral oophorectomy as treatment for ovarian cancer or bilateral oophorectomy as treatment for another estrogen-related cancer.[8]

Referent Cohort

The records-linkage system of the Rochester Epidemiology Project provided the list of residents from which potential referent women were drawn. This list has been shown to be complete when compared with a random-digit-dialing telephone sample and with the census.[22] For each woman in the unilateral or in the bilateral oophorectomy cohorts, we defined the year of surgery as the index year. We then used simple random sampling to select one woman from the complete Olmsted County population with the same year of birth who had survived without any oophorectomy to the index year. However, hysterectomy without oophorectomy was not an exclusion criterion, and referent women were not required to be premenopausal in the index year. All women in the population who met these criteria were considered eligible regardless of any possible diseases or risk factors (population-based referent sample).

Follow-up Procedures

The primary objective of follow-up in the Mayo Clinic Cohort Study of Oophorectomy and Aging was to detect incident cases of parkinsonism and dementia. Methods for tracking participants and for detecting parkinsonism or dementia are reported elsewhere.[8,15-18] We describe here only the methods relevant to the assessment of causes of death. All study procedures were approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center. Both the oophorectomy and the referent cohorts were followed using three methods.

First, women were interviewed via telephone using a standardized questionnaire to assess their vital status and the presence of the diseases of interest. The telephone contact was direct whenever possible and conducted by one of six specifically trained research assistants. For deceased or incapacitated women (eg, deaf, cognitively impaired, or terminally ill), we contacted a surrogate informant (proxy interview). Second, independent of the telephone contact, all women were followed passively through review of inpatient and outpatient medical records in the records-linkage system of the Rochester Epidemiology Project.[22] Finally, vital status was assessed using state-specific or national death indices. For each deceased woman, we obtained a copy of the death certificate from either the records-linkage system or the vital statistics offices of individual states. When this was not possible, we obtained death certificate information from the National Death Index (NDI Plus; National Center for Health Statistics, Hyattsville, MD). A trained medical indexing clerk recoded all causes of death listed on the death certificates (underlying, intermediate, immediate, and other major conditions) using the *International Classification of Diseases, Adapted Codes for Hospitals* (this is a modification of the *International Classification of Diseases* [ICD], *Eighth Revision*).[23] The clerk was kept unaware of the oophorectomy status of deceased women to prevent bias.

We adapted the classification of cardiovascular diseases used by the American Heart Association to produce a set of mutually exclusive categories including coronary heart disease, non-coronary heart disease, and non-cardiac circulatory disease.[24] To allow comparison with other studies, Table 1 shows the list of ICD-9 and ICD-10 codes corresponding to each of the cardiovascular categories.[25]

Table 1. American Heart Association Classification of CVD and Corresponding Icd Causes of Death

CVD categories[a]	ICD-9[b]	ICD-10[b]	ICD blocks[b]
Total CVD	390-459	100-199	All circulatory diseases
CHD	410-414	120-125	Ischemic heart diseases
Non-CHD disease of the heart	390-398, 402, 404, 405, 415-429	100-109, 111, 113, 126-151	Acute rheumatic fever; chronic rheumatic heart disease; hypertensive heart diseases; pulmonary circulatory diseases; other forms of heart disease
Non-cardiac circulatory diseases	401, 403, 430-459	110, 112, 115, 152-199	Cerebrovascular diseases; other hypertensive heart diseases (not included elsewhere); diseases of the arteries, arterioles, and capillaries; diseases of the veins, lymphatic vessels, and lymph nodes; other and unspecified disorders of the circulatory system

CVD, cardiovascular disease; CHD, coronary heart disease; ICD, *International Classification of Diseases*.
[a]Adapted from the American Heart Association classification of cardiovascular diseases to produce a set of mutually exclusive groups of cardiovascular deaths.[25]
[b]The full listing of the *International Classification of Diseases, Adopted Codes for Hospitals* codes (a modification of ICD-8) used in this study is available from the authors upon request (the list is too extensive to be summarized easily in the table). The ICD-9 and ICD-10 codes are shown to allow comparison with other studies.

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Statistical Analysis

We obtained survival curves using the Kaplan-Meier method and estimated hazard ratios (HRs) using Cox proportional hazards models. These models allowed for complete age adjustment by using age as the time scale. The assumption of proportional hazards was assessed by graphical methods and by introducing a time-dependent coefficient in the Cox models.[26]

We first considered deaths with cardiovascular diseases listed as the underlying cause. Second, we considered all deaths with cardiovascular diseases listed anywhere on the death certificate (including underlying, intermediate, and immediate causes of death and other major conditions contributing to death). Because the beneficial or harmful effects of estrogen may vary across vascular beds, we also considered mortality specific for coronary heart disease, cerebrovascular disease, and for all cardiovascular diseases, excluding cerebrovascular disease.[27]

Analyses were conducted overall and in strata defined by age at oophorectomy (or at index year) and by surgical indication. To simplify the presentation of results, we used arbitrary prespecified cutoffs for age (ie, <45, 45-50, and >50 y) rather than distribution-related cutoffs (eg, tertiles). However, the cutoff at age 50 years is also clinically relevant because it is the approximate median age of natural menopause.[2] We also conducted analyses accounting for the combined effect of age at bilateral oophorectomy and length of estrogen treatment after the surgery. Information about treatment with oral or transdermal estrogen in women who underwent bilateral oophorectomy was abstracted from the inpatient and outpatient medical records in the records-linkage system.[22]

To test the hypothesis that irreversible vascular damage may occur only many years after bilateral oophorectomy, we conducted sensitivity analyses excluding all women followed for less than 10 years. Finally, because data about specific cardiovascular risk factors that were present at the index year were not available, we used hysterectomy as a surrogate marker.[12,28] To address the possible confounding effect of hysterectomy and its associated adverse cardiovascular risk profile, we conducted analyses contrasting women who underwent bilateral oophorectomy (most of whom also had hysterectomy) with women who underwent hysterectomy with one ovary preserved (from the unilateral oophorectomy cohort). All analyses were completed using SAS version 8.2 (SAS Institute, Cary, NC), and tests of statistical significance were conducted at the two-tailed α level of 0.05.

Results

Study Sample

Among the 1,274 women with unilateral oophorectomy included in the study, 942 (74%) underwent oophorectomy because of a benign ovarian condition (cyst in 314, endometriosis in 206, benign tumor in 159, inflammation in 104, other rare conditions in 159), whereas the remaining 332 (26%) women did not have a specified indication. A total of 826 (65%) women underwent oophorectomy at the time of hysterectomy and 43 (3%) underwent hysterectomy before oophorectomy. The women in the unilateral oophorectomy cohort were followed for a median of 29.5 years (range, 54 d-54.6 y); a total of 304 women died during follow-up, and 297 (98%) death certificates were obtained. The 297 death certificates yielded 1,106 diagnostic codes (median, 3

codes per woman; range, 1-14). Three women died within 1 year of the oophorectomy. Of the 1,274 women included in these analyses, 628 (49%) were interviewed directly, 190 (15%) were interviewed via proxy, and the remaining 456 (36%) had only passive follow-up information.

Among the 1,091 women with bilateral oophorectomy included in the study (77 women with a second unilateral oophorectomy), 554 (51%) underwent oophorectomy because of a benign ovarian condition (cyst in 144, endometriosis in 227, benign tumor in 77, inflammation in 50, other rare conditions in 56), whereas the remaining 537 (49%) underwent oophorectomy to prevent ovarian cancer (prophylactic bilateral oophorectomy). A total of 1,031 (95%) women underwent oophorectomy at the time of hysterectomy and 32 (3%) underwent hysterectomy before oophorectomy. The women in the bilateral oophorectomy cohort were followed for a median of 25.0 years (range, 4 d-53.8 y); a total of 360 women died during follow-up, and 358 (99%) death certificates were obtained. The 358 death certificates yielded 1,275 diagnostic codes (median, 3 codes per woman; range, 1-10). Nine women died within 1 year of the oophorectomy. Of the 1,091 women included in these analyses, 452 (41%) were interviewed directly, 232 (21%) were interviewed via proxy, and the remaining 407 (37%) had only passive follow-up information.

Among the 2,383 referent women included in the study, 57 underwent subsequent bilateral oophorectomy for a noncancer indication between 1950 and 1987. These 57 women were included in the referent cohort before oophorectomy and in the bilateral oophorectomy cohort after the surgery. An additional seven referent women underwent subsequent bilateral oophorectomy for a cancer indication, and they were censored alive at the time of oophorectomy. Finally, 31 women underwent subsequent unilateral oophorectomy between 1950 and 1987 and were included in the referent cohort before oophorectomy and in the unilateral oophorectomy cohort after the surgery. Altogether, referent women were followed for a median of 26.4 years (range, 66 d-55.1 y); 628 of these women died during follow-up, and 618 (98%) death certificates were obtained. The 618 death certificates yielded 2,284 diagnostic codes (median, 3 codes per woman; range, 1-14). Of the 2,383 women included, 1,037 (44%) were interviewed directly, 443 (19%) were interviewed via proxy, and 903 (38%) had only passive follow-up information.

Mortality From All Causes

Our results for mortality from all causes were reported elsewhere.[8] In brief, mortality was not increased in women who underwent bilateral oophorectomy compared with referent women in the overall analyses. However, mortality was significantly higher in women who underwent prophylactic bilateral oophorectomy before the age of 45 years than in referent women (HR, 1.67; 95% CI, 1.16-2.40; $P = 0.006$).[8] This increased mortality was seen mainly in women who were not treated with estrogen through age 45 years or longer. In contrast, no increased mortality was found in women who underwent unilateral oophorectomy in either overall or stratified analyses.[8]

Overall Cardiovascular Disease Mortality

Table 2 shows the survival analyses restricted to cardiovascular disease in women who underwent unilateral oophorectomy compared with referent women. Women who underwent unilateral oophorectomy experienced a reduced cardiovascular mortality in analyses considering only one underlying cause of death for each woman and in analyses considering diseases listed anywhere on the death certificate. Results were similar for women who underwent unilateral oophorectomy before age 45 years; however, the associations were not statistically significant. The effect of unilateral oophorectomy was not modified significantly by the indication for the surgery or by concurrent hysterectomy.

Table 2. Mortality Associated with CVD After Unilateral Oophorectomy

Cohort or stratum	Women at risk	Person-years of follow-up	Total deaths, n	CVD as underlying cause of death[a]			CVD listed anywhere on the death certificate[b]		
				Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	2,383	62,285	628	216 (9.1)	1.00 (reference)	—	334 (14.0)	1.00 (reference)	—
Oophorectomy	1,274	37,499	304	82 (6.4)	0.70 (0.55-0.91)	0.01	148 (11.6)	0.82 (0.67-0.99)	0.04
No specified indication	332	9,131	86	20 (6.0)	0.68 (0.43-1.08)	0.10	35 (10.5)	0.77 (0.54-1.09)[c]	0.13
Benign conditions	942	28,368	218	62 (6.6)	0.71 (0.54-0.95)	0.02	113 (12.0)	0.84 (0.68-1.04)[c]	0.10
With hysterectomy	869	25,023	230	62 (7.1)	0.67 (0.51-0.89)	0.01	115 (13.2)	0.80 (0.65-0.99)[d]	0.04
Without hysterectomy	405	12,476	74	20 (4.9)	0.85 (0.54-1.34)	0.48	33 (8.2)	0.91 (0.63-1.30)[d]	0.60
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	1,417	38,106	229	68 (4.8)	1.00 (reference)	—	104 (7.3)	1.00 (reference)	—
Oophorectomy	991	29,225	159	39 (3.9)	0.73 (0.49-1.08)	0.11	71 (7.2)	0.85 (0.63-1.15)	0.30
No specified indication	218	5,948	32	5 (2.3)	0.52 (0.21-1.29)	0.16	11 (5.1)	0.75 (0.40-1.39)	0.36
Benign conditions	773	23,277	127	34 (4.4)	0.77 (0.51-1.16)	0.21	60 (7.8)	0.87 (0.63-1.20)	0.39
With hysterectomy	628	17,990	109	30 (4.8)	0.77 (0.50-1.18)	0.23	54 (8.6)	0.89 (0.64-1.24)	0.49
Without hysterectomy	363	11,235	50	9 (2.5)	0.62 (0.31-1.24)	0.18	17 (4.7)	0.76 (0.46-1.28)	0.30
Middle and older (≥45 y)									
Referent women	966	24,179	399	148 (15.3)	1.00 (reference)	—	230 (23.8)	1.00 (reference)	—
Oophorectomy	283	8,275	145	43 (15.2)	0.70 (0.50-0.99)	0.04	77 (27.2)	0.80 (0.62-1.04)	0.09

CVD, cardiovascular disease; HR, hazard ratio.
[a]CVD cause of death listed on the death certificate as the underlying cause of death.
[b]CVD cause of death listed anywhere on the death certificate and including underlying, intermediate, immediate, or other major conditions contributing to death.
[c]A formal test of interaction was not significant ($P = 0.61$).
[d]A formal test of interaction was not significant ($P = 0.43$).

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Table 3 shows survival analyses restricted to cardiovascular disease in women who underwent bilateral oophorectomy compared with referent women. Analyses using only one underlying cause of death for each woman did not reveal any association overall or in strata by indication for the oophorectomy or by age at oophorectomy. In contrast, women who underwent bilateral oophorectomy before age 45 years had a significantly increased mortality associated with cardiovascular diseases compared with referent women when considering all conditions listed anywhere on the death certificate. In particular, women who underwent oophorectomy before age 45 years but were treated with estrogen from the time of the surgery through age 45 years or longer had no increased mortality (HR, 0.65; 95% CI, 0.30-1.41; $P = 0.28$), whereas women who were not treated after the surgery or interrupted their treatment before age 45 years experienced increased mortality (HR, 1.84; 95% CI, 1.27-2.68; $P = 0.001$; Fig. 1). Although these analyses were based on small numbers, a formal test for difference of mortality across estrogen treatment strata was significant (test of interaction, $P = 0.01$).

Table 3. Mortality Associated with CVD After Bilateral Oophorectomy

Cohort or stratum	Women at risk	Person-years of follow-up	Total deaths, n	CVD as underlying cause of death[a]			CVD listed anywhere on the death certificate[b]		
				Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	2,383	62,285	628	216 (9.1)	1.00 (reference)	—	334 (14.0)	1.00 (reference)	—
Oophorectomy	1,091	27,864	360	106 (9.7)	0.87 (0.69-1.10)	0.24	175 (16.0)	0.94 (0.78-1.13)	0.49
Prophylactic	537	12,960	184	54 (10.1)	0.83 (0.61-1.12)	0.22	87 (16.2)	0.87 (0.69-1.11)	0.27
Benign conditions	554	14,904	176	52 (9.4)	0.91 (0.67-1.23)	0.54	88 (15.9)	1.00 (0.79-1.27)	0.98
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	1,417	38,106	229	68 (4.8)	1.00 (reference)	—	104 (7.3)	1.00 (reference)	—
Oophorectomy	413	11,179	94	26 (6.3)	1.25 (0.79-1.96)	0.34	45 (10.9)	1.44 (1.01-2.05)[c]	0.04
Estrogen given from surgery until age 45 y or longer	151	4,167	20	5 (3.3)	0.68 (0.27-1.71)	0.42	7 (4.6)	0.65 (0.30-1.41)[d]	0.28
Estrogen not given or discontinued before age 45 y	262	7,012	74	21 (8.0)	1.54 (0.94-2.52)	0.08	38 (14.5)	1.84 (1.27-2.68)[d]	0.001
Prophylactic	124	3,164	33	9 (7.3)	1.57 (0.78-3.16)	0.20	15 (12.1)	1.73 (1.00-2.98)	0.049
Benign conditions	289	8,015	61	17 (5.9)	1.12 (0.66-1.91)	0.68	30 (10.4)	1.32 (0.88-1.99)	0.18
Middle (45-50 y)									
Referent women	645	16,683	240	88 (13.6)	1.00 (reference)	—	136 (21.1)	1.00 (reference)	—
Oophorectomy	430	10,745	148	39 (9.1)	0.72 (0.49-1.05)	0.09	70 (16.3)	0.84 (0.63-1.12)	0.24
Estrogen given from surgery until age 50 y or longer	160	3,777	35	7 (4.4)	0.47 (0.22-1.01)	0.05	14 (8.8)	0.61 (0.35-1.06)[e]	0.08
Estrogen not given or discontinued before age 50 y	270	6,968	113	32 (11.9)	0.81 (0.54-1.22)	0.32	56 (20.7)	0.93 (0.68-1.27)[e]	0.64
Older (>50 y)									
Referent women	321	7,496	159	60 (18.7)	1.00 (reference)	—	94 (29.3)	1.00 (reference)	—
Oophorectomy	248	5,940	118	41 (16.5)	0.86 (0.58-1.29)	0.47	60 (24.2)	0.82 (0.59-1.14)	0.24

CVD, cardiovascular disease; HR, hazard ratio.

[a]CVD cause of death listed on the death certificate as the underlying cause of death.

[b]CVD cause of death listed anywhere on the death certificate and including underlying, intermediate, immediate, or other major conditions contributing to death.

[c]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.38; 95% CI, 0.95-1.99; $P = 0.09$). A sensitivity analysis contrasting women who underwent bilateral oophorectomy with the 628 women who underwent hysterectomy (from the unilateral oophorectomy cohort) yielded similar results (HR, 1.67; 95% CI, 1.11-2.50; $P = 0.01$).

[d]A formal test of interaction was significant ($P = 0.01$).

[e]A formal test of interaction was not significant ($P = 0.16$).

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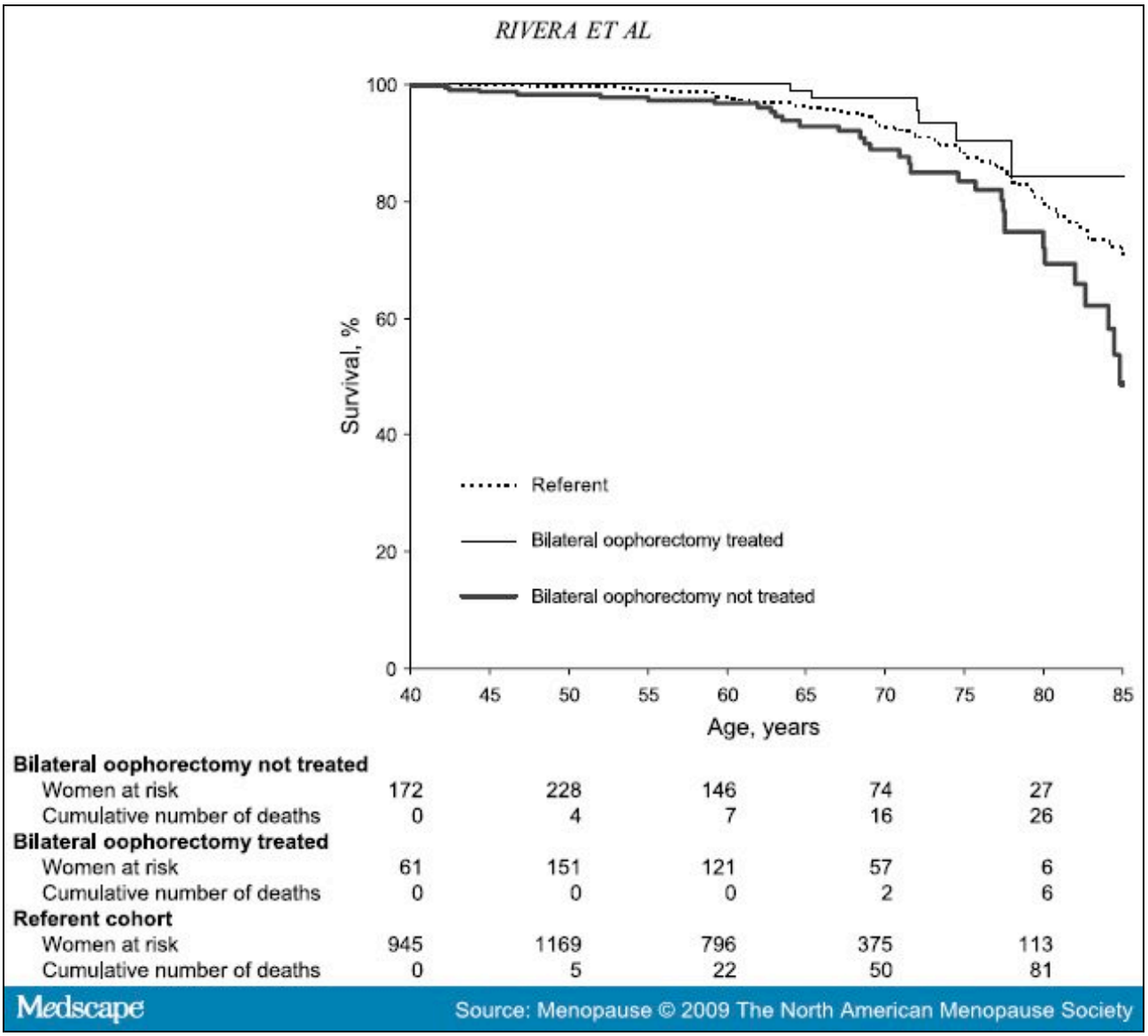

Figure 1. Cardiovascular mortality in women who underwent bilateral oophorectomy before age 45 years and were or were not treated with estrogen through age 45 years or longer. All diagnoses reported anywhere on the death certificate were considered.

A sensitivity analysis excluding all deaths occurring within 10 years of follow-up after bilateral oophorectomy yielded results similar to those of the primary analysis (Table 3 , footnote c). In addition, the association between bilateral oophorectomy and risk of cardiovascular death was similar in a sensitivity analysis that contrasted women who underwent bilateral oophorectomy with women who underwent hysterectomy (from the unilateral oophorectomy cohort; Table 3 , footnote c).

Table 3. Mortality Associated with CVD After Bilateral Oophorectomy

Cohort or stratum	Women at risk	Person-years of follow-up	Total deaths, n	CVD as underlying cause of death[a]			CVD listed anywhere on the death certificate[b]		
				Deaths, n (%)	HR (95% CI)	P	Deaths, n (%)	HR (95% CI)	P
Overall analyses									
Referent women	2,383	62,285	628	216 (9.1)	1.00 (reference)	—	334 (14.0)	1.00 (reference)	—
Oophorectomy	1,091	27,864	360	106 (9.7)	0.87 (0.69-1.10)	0.24	175 (16.0)	0.94 (0.78-1.13)	0.49
Prophylactic	537	12,960	184	54 (10.1)	0.83 (0.61-1.12)	0.22	87 (16.2)	0.87 (0.69-1.11)	0.27
Benign conditions	554	14,904	176	52 (9.4)	0.91 (0.67-1.23)	0.54	88 (15.9)	1.00 (0.79-1.27)	0.98
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[c]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.38; 95% CI, 0.95-1.99; $P = 0.09$). A sensitivity analysis contrasting women who underwent bilateral oophorectomy with the 628 women who underwent hysterectomy (from the unilateral oophorectomy cohort) yielded similar results (HR, 1.67; 95% CI, 1.11-2.50; $P = 0.01$).
[d]A formal test of interaction was significant ($P = 0.01$).
[e]A formal test of interaction was not significant ($P = 0.16$).

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Oophorectomy	1,091	27,864	360	106 (9.7)	0.87 (0.69-1.10)	0.24	175 (16.0)	0.94 (0.78-1.13)	0.49
Prophylactic	537	12,960	184	54 (10.1)	0.83 (0.61-1.12)	0.22	87 (16.2)	0.87 (0.69-1.11)	0.27
Benign conditions	554	14,904	176	52 (9.4)	0.91 (0.67-1.23)	0.54	88 (15.9)	1.00 (0.79-1.27)	0.98
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	1,417	38,106	229	68 (4.8)	1.00 (reference)	—	104 (7.3)	1.00 (reference)	—
Oophorectomy	413	11,179	94	26 (6.3)	1.25 (0.79-1.96)	0.34	45 (10.9)	1.44 (1.01-2.05)[c]	0.04
Estrogen given from surgery until age 45 y or longer	151	4,167	20	5 (3.3)	0.68 (0.27-1.71)	0.42	7 (4.6)	0.65 (0.30-1.41)[d]	0.28
Estrogen not given or discontinued before age 45 y	262	7,012	74	21 (8.0)	1.54 (0.94-2.52)	0.08	38 (14.5)	1.84 (1.27-2.68)[d]	0.001
Prophylactic	124	3,164	33	9 (7.3)	1.57 (0.78-3.16)	0.20	15 (12.1)	1.73 (1.00-2.98)	0.049
Benign conditions	289	8,015	61	17 (5.9)	1.12 (0.66-1.91)	0.68	30 (10.4)	1.32 (0.88-1.99)	0.18
Middle (45-50 y)									
Referent women	645	16,683	240	88 (13.6)	1.00 (reference)	—	136 (21.1)	1.00 (reference)	—
Oophorectomy	430	10,745	148	39 (9.1)	0.72 (0.49-1.05)	0.09	70 (16.3)	0.84 (0.63-1.12)	0.24
Estrogen given from surgery until age 50 y or longer	160	3,777	35	7 (4.4)	0.47 (0.22-1.01)	0.05	14 (8.8)	0.61 (0.35-1.06)[e]	0.08
Estrogen not given or discontinued before age 50 y	270	6,968	113	32 (11.9)	0.81 (0.54-1.22)	0.32	56 (20.7)	0.93 (0.68-1.27)[e]	0.64
Older (>50 y)									
Referent women	321	7,496	159	60 (18.7)	1.00 (reference)	—	94 (29.3)	1.00 (reference)	—
Oophorectomy	248	5,940	118	41 (16.5)	0.86 (0.58-1.29)	0.47	60 (24.2)	0.82 (0.59-1.14)	0.24

CVD, cardiovascular disease; HR, hazard ratio.
[a]CVD cause of death listed on the death certificate as the underlying cause of death.
[b]CVD cause of death listed anywhere on the death certificate and including underlying, intermediate, immediate, or other major conditions contributing to death.
[c]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.38; 95% CI, 0.95-1.99; $P = 0.09$). A sensitivity analysis contrasting women who underwent bilateral oophorectomy with the 628 women who underwent hysterectomy (from the unilateral oophorectomy cohort) yielded similar results (HR, 1.67; 95% CI, 1.11-2.50; $P = 0.01$).
[d]A formal test of interaction was significant ($P = 0.01$).
[e]A formal test of interaction was not significant ($P = 0.16$).

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Specific Cardiovascular Causes of Death

Table 4 shows survival analyses in women who underwent bilateral oophorectomy conducted separately for coronary heart disease, cerebrovascular disease, and for all cardiovascular diseases, excluding cerebrovascular disease. We considered causes of death listed anywhere on the death certificate. Overall, women who had bilateral oophorectomy did not experience an increased mortality associated with coronary heart disease or cerebrovascular disease considered separately. In contrast, we found a significantly increased risk of death associated with all cardiovascular diseases after excluding cerebrovascular disease in women with bilateral oophorectomy before age 45 years. A sensitivity analysis excluding all deaths occurring within 10 years of follow-up yielded similar findings (Table 4 , footnote b).

Table 4. Mortality by Type of Cardiovascular Disease After Bilateral Oophorectomy (Diagnoses Listed Anywhere on Death Certificates)

Cohort or stratum	Coronary heart disease			Cerebrovascular disease[a]			Total cardiovascular diseases excluding cerebrovascular		
	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	163 (6.8)	1.00 (reference)	—	69 (2.9)	1.00 (reference)	—	265 (11.1)	1.00 (reference)	—
Oophorectomy	77 (7.1)	0.84 (0.64-1.11)	0.21	35 (3.2)	0.90 (0.60-1.35)	0.60	140 (12.8)	0.95 (0.77-1.16)	0.61
Prophylactic	42 (7.8)	0.86 (0.61-1.21)	0.39	21 (3.9)	1.00 (0.61-1.63)	1.0	66 (12.3)	0.84 (0.64-1.10)	0.21
Benign conditions	35 (6.3)	0.82 (0.57-1.18)	0.28	14 (2.5)	0.77 (0.43-1.36)	0.36	74 (13.4)	1.07 (0.82-1.38)	0.63
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	42 (3.0)	1.00 (reference)	—	22 (1.6)	1.00 (reference)	—	82 (5.8)	1.00 (reference)	—
Oophorectomy	18 (4.4)	1.40 (0.80-2.44)	0.24	8 (1.9)	1.22 (0.54-2.74)	0.64	37 (9.0)	1.50 (1.02-2.23)[b]	0.04
Middle (45-50 y)									
Referent women	76 (11.8)	1.00 (reference)	—	30 (4.7)	1.00 (reference)	—	106 (16.4)	1.00 (reference)	—
Oophorectomy	30 (7.0)	0.65 (0.43-1.00)	0.049	15 (3.5)	0.77 (0.41-1.45)	0.42	55 (12.8)	0.86 (0.62-1.19)	0.36
Older (>50 y)									
Referent women	45 (14.0)	1.00 (reference)	—	17 (5.3)	1.00 (reference)	—	77 (24.0)	1.00 (reference)	—
Oophorectomy	29 (11.7)	0.80 (0.50-1.29)	0.36	12 (4.8)	0.94 (0.45-1.98)	0.87	48 (19.4)	0.80 (0.55-1.15)	0.22

[a]Cerebrovascular diseases include ischemic stroke (thrombotic, embolic, and lacunar infarcts) and hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage). Transient ischemic attacks and cerebrovascular events due to trauma, blood disorders, or malignancy were excluded.
[b]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.44; 95% CI, 0.96-2.17; $P = 0.08$).

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Table 4. Mortality by Type of Cardiovascular Disease After Bilateral Oophorectomy (Diagnoses Listed Anywhere on Death Certificates)

Cohort or stratum	Coronary heart disease			Cerebrovascular disease[a]			Total cardiovascular diseases excluding cerebrovascular		
	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	163 (6.8)	1.00 (reference)	—	69 (2.9)	1.00 (reference)	—	265 (11.1)	1.00 (reference)	—
Oophorectomy	77 (7.1)	0.84 (0.64-1.11)	0.21	35 (3.2)	0.90 (0.60-1.35)	0.60	140 (12.8)	0.95 (0.77-1.16)	0.61
Prophylactic	42 (7.8)	0.86 (0.61-1.21)	0.39	21 (3.9)	1.00 (0.61-1.63)	1.0	66 (12.3)	0.84 (0.64-1.10)	0.21
Benign conditions	35 (6.3)	0.82 (0.57-1.18)	0.28	14 (2.5)	0.77 (0.43-1.36)	0.36	74 (13.4)	1.07 (0.82-1.38)	0.63
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	42 (3.0)	1.00 (reference)	—	22 (1.6)	1.00 (reference)	—	82 (5.8)	1.00 (reference)	—
Oophorectomy	18 (4.4)	1.40 (0.80-2.44)	0.24	8 (1.9)	1.22 (0.54-2.74)	0.64	37 (9.0)	1.50 (1.02-2.23)[b]	0.04
Middle (45-50 y)									
Referent women	76 (11.8)	1.00 (reference)	—	30 (4.7)	1.00 (reference)	—	106 (16.4)	1.00 (reference)	—
Oophorectomy	30 (7.0)	0.65 (0.43-1.00)	0.049	15 (3.5)	0.77 (0.41-1.45)	0.42	55 (12.8)	0.86 (0.62-1.19)	0.36
Older (>50 y)									
Referent women	45 (14.0)	1.00 (reference)	—	17 (5.3)	1.00 (reference)	—	77 (24.0)	1.00 (reference)	—
Oophorectomy	29 (11.7)	0.80 (0.50-1.29)	0.36	12 (4.8)	0.94 (0.45-1.98)	0.87	48 (19.4)	0.80 (0.55-1.15)	0.22

[a]Cerebrovascular diseases include ischemic stroke (thrombotic, embolic, and lacunar infarcts) and hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage). Transient ischemic attacks and cerebrovascular events due to trauma, blood disorders, or malignancy were excluded.
[b]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.44; 95% CI, 0.96-2.17; $P = 0.08$).

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Discussion

Our cohort study provides a unique natural experiment that replicates in humans the oophorectomy experiments originally conducted in animals.[29-33] This was ethically possible because in the past decades, a large percentage of women underwent early bilateral oophorectomy. Our study specifically focused on mortality that occurred many years after the time of bilateral oophorectomy (20-30 years). Therefore, our study addressed questions that cannot be feasibly tested by clinical trials with shorter

duration of follow-up.

From a clinical perspective, our findings suggest that women who underwent bilateral oophorectomy at a young age are at increased risk of cardiovascular death, especially of cardiac death. This increased mortality may be attenuated by adequate estrogen treatment. Our findings provide new evidence to guide the individualized assessment of the risks and benefits of prophylactic bilateraloophorectomy in young women.[1,4-6,8,14] This preventive practice currently involves approximately 4.5 million women older than 55 years living in the United States who have undergone bilateral oophorectomy before reaching natural menopause.[28,34]

In addition, our findings provide observational evidence for a long-term cardiovascular protective effect of estrogen either naturally produced by the ovaries or given as treatment to women who underwent bilateral oophorectomy at younger ages. These findings emphasize the importance of estrogen treatment after the surgery.[6,9-14] We focused our analyses on age at estrogen deficiency rather than on the length of estrogen treatment after the surgery to study the combined effects of age at the surgery and length of treatment.

Our findings are indirectly supported by findings from previous studies that addressed related issues. Several studies have shown increased cardiovascular mortality in women who experienced early menopause (before age 45) from either natural or medical causes,[35-40] and a statistical model has linked prophylactic bilateral oophorectomy before age 65 years with an increase in overall mortality and coronary heart disease mortality.[1,4,5] Similarly, in the Women's Health Initiative Observational Study, hysterectomy plus oophorectomy performed over a broad age range was a significant predictor of cardiovascular disease during a short-term follow-up.[28] Recent analyses from the Women's Health Initiative Coronary Artery Calcium Study showed an increased risk of subclinical coronary artery disease in women who underwent both hysterectomy and bilateral oophorectomy and were not treated with estrogen compared with women who underwent hysterectomy alone. The increased risk was independent of traditional cardiovascular risk factors.[12]

Our results for estrogen treatment after bilateral oophorectomy are consistent both with findings from previous clinical studies[40-44] and with findings from animal studies. Primates that underwent premenopausal oophorectomy and did not receive exogenous estrogen had significantly accelerated atherosclerosis compared with those that did not have oophorectomy.[29,30] In contrast, estrogen lost its cardioprotective effects in primates when therapy was initiated in the late postmenopausal years.[31,32] A similar detrimental effect of estrogen initiated at later ages was established in women by the Women's Health Initiative clinical trials.[43,44] The hypothesis that the effect of estrogen on cardiovascular disease varies with age is known as the timing hypothesis.[43-46]

Strengths

There are several strengths to our study. First, our referent cohort was representative of the general population as demonstrated by a comparison with the life tables of Minnesota white women in corresponding census periods (628 observed deaths vs 628.2 expected deaths; $P = 0.99$).[8] This comparison also confirms that our methods to capture mortality were complete. Second, oophorectomy was documented historically in medical records, and no interview or recall of past surgical events was required.[47] Similarly, we were able to abstract information regarding estrogen treatment after bilateral oophorectomy from historical medical records, and no recall of past estrogen use was required.[47] Third, the women in the bilateral oophorectomy cohort were followed for a median of 25.0 years and those in the referent cohort were followed for a median of 26.4 years. Thus, we studied the long-term outcomes associated with bilateral oophorectomy. Fourth, the risk of misclassification of the underlying cause of death as coded on routine death certificates was reduced by considering all conditions listed anywhere on the death certificate for each woman. In addition, it has been demonstrated that the positive predictive value of a death certificate diagnosis of coronary heart disease in Olmsted County is high, with only a 5% underestimation of true heart disease rates.[48]

Limitations

There are also limitations to our study. First, because of funding limitations, we could not study the incidence of cardiovascular disease using direct or proxy interviews or using medical record information from the records-linkage system. The use of cardiovascular disease mentioned anywhere on the death certificates was only a surrogate measure of the full manifestation of

nonfatal and fatal cardiovascular disease. On the other hand, the consideration of all diagnoses listed anywhere on the death certificate was a major improvement from the use of only one underlying cause of death for each woman.

Second, the association between bilateral oophorectomy and cardiovascular mortality may be confounded by socioeconomic status. In particular, lower socioeconomic status may increase the probability of undergoing a bilateral oophorectomy,[49] decrease the probability of receiving adequate estrogen treatment after the oophorectomy,[50] and independently increase cardiovascular mortality.[51] Unfortunately, information on income or education was not available for the overall cohorts. However, the population of Olmsted County is almost entirely middle class, is well educated, and has excellent access to medical care.[22] In addition, the results were similar regardless of the indication for the bilateral oophorectomy. Because socioeconomic status may play a bigger role in a woman's decision to undergo bilateral oophorectomy for prophylaxis rather than as treatment for a benign ovarian condition, these stratified analyses provide evidence against a major confounding effect (Table 3 and Table 4). As in any other cohort study, it was impossible to rule out other unrecognized confounding variables.

Table 3. Mortality Associated with CVD After Bilateral Oophorectomy

				CVD as underlying cause of death[a]			CVD listed anywhere on the death certificate[b]		
Cohort or stratum	Women at risk	Person-years of follow-up	Total deaths, n	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	2,383	62,285	628	216 (9.1)	1.00 (reference)	—	334 (14.0)	1.00 (reference)	—
Oophorectomy	1,091	27,864	360	106 (9.7)	0.87 (0.69-1.10)	0.24	175 (16.0)	0.94 (0.78-1.13)	0.49
Prophylactic	537	12,960	184	54 (10.1)	0.83 (0.61-1.12)	0.22	87 (16.2)	0.87 (0.69-1.11)	0.27
Benign conditions	554	14,904	176	52 (9.4)	0.91 (0.67-1.23)	0.54	88 (15.9)	1.00 (0.79-1.27)	0.98
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	1,417	38,106	229	68 (4.8)	1.00 (reference)	—	104 (7.3)	1.00 (reference)	—
Oophorectomy	413	11,179	94	26 (6.3)	1.25 (0.79-1.96)	0.34	45 (10.9)	1.44 (1.01-2.05)[c]	0.04
Estrogen given from surgery until age 45 y or longer	151	4,167	20	5 (3.3)	0.68 (0.27-1.71)	0.42	7 (4.6)	0.65 (0.30-1.41)[d]	0.28
Estrogen not given or discontinued before age 45 y	262	7,012	74	21 (8.0)	1.54 (0.94-2.52)	0.08	38 (14.5)	1.84 (1.27-2.68)[d]	0.001
Prophylactic	124	3,164	33	9 (7.3)	1.57 (0.78-3.16)	0.20	15 (12.1)	1.73 (1.00-2.98)	0.049
Benign conditions	289	8,015	61	17 (5.9)	1.12 (0.66-1.91)	0.68	30 (10.4)	1.32 (0.88-1.99)	0.18
Middle (45-50 y)									
Referent women	645	16,683	240	88 (13.6)	1.00 (reference)	—	136 (21.1)	1.00 (reference)	—
Oophorectomy	430	10,745	148	39 (9.1)	0.72 (0.49-1.05)	0.09	70 (16.3)	0.84 (0.63-1.12)	0.24
Estrogen given from surgery until age 50 y or longer	160	3,777	35	7 (4.4)	0.47 (0.22-1.01)	0.05	14 (8.8)	0.61 (0.35-1.06)[e]	0.08
Estrogen not given or discontinued before age 50 y	270	6,968	113	32 (11.9)	0.81 (0.54-1.22)	0.32	56 (20.7)	0.93 (0.68-1.27)[e]	0.64
Older (>50 y)									
Referent women	321	7,496	159	60 (18.7)	1.00 (reference)	—	94 (29.3)	1.00 (reference)	—
Oophorectomy	248	5,940	118	41 (16.5)	0.86 (0.58-1.29)	0.47	60 (24.2)	0.82 (0.59-1.14)	0.24

CVD, cardiovascular disease; HR, hazard ratio.
[a]CVD cause of death listed on the death certificate as the underlying cause of death.
[b]CVD cause of death listed anywhere on the death certificate and including underlying, intermediate, immediate, or other major conditions contributing to death.
[c]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.38; 95% CI, 0.95-1.99; $P = 0.09$). A sensitivity analysis contrasting women who underwent bilateral oophorectomy with the 628 women who underwent hysterectomy (from the unilateral oophorectomy cohort) yielded similar results (HR, 1.67; 95% CI, 1.11-2.50; $P = 0.01$).
[d]A formal test of interaction was significant ($P = 0.01$).
[e]A formal test of interaction was not significant ($P = 0.16$).

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Table 4. Mortality by Type of Cardiovascular Disease After Bilateral Oophorectomy (Diagnoses Listed Anywhere on Death Certificates)

Cohort or stratum	Coronary heart disease			Cerebrovascular disease[a]			Total cardiovascular diseases excluding cerebrovascular		
	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*	Deaths, n (%)	HR (95% CI)	*P*
Overall analyses									
Referent women	163 (6.8)	1.00 (reference)	—	69 (2.9)	1.00 (reference)	—	265 (11.1)	1.00 (reference)	—
Oophorectomy	77 (7.1)	0.84 (0.64-1.11)	0.21	35 (3.2)	0.90 (0.60-1.35)	0.60	140 (12.8)	0.95 (0.77-1.16)	0.61
Prophylactic	42 (7.8)	0.86 (0.61-1.21)	0.39	21 (3.9)	1.00 (0.61-1.63)	1.0	66 (12.3)	0.84 (0.64-1.10)	0.21
Benign conditions	35 (6.3)	0.82 (0.57-1.18)	0.28	14 (2.5)	0.77 (0.43-1.36)	0.36	74 (13.4)	1.07 (0.82-1.38)	0.63
Analyses stratified by age at oophorectomy or index year									
Younger (<45 y)									
Referent women	42 (3.0)	1.00 (reference)	—	22 (1.6)	1.00 (reference)	—	82 (5.8)	1.00 (reference)	—
Oophorectomy	18 (4.4)	1.40 (0.80-2.44)	0.24	8 (1.9)	1.22 (0.54-2.74)	0.64	37 (9.0)	1.50 (1.02-2.23)[b]	0.04
Middle (45-50 y)									
Referent women	76 (11.8)	1.00 (reference)	—	30 (4.7)	1.00 (reference)	—	106 (16.4)	1.00 (reference)	—
Oophorectomy	30 (7.0)	0.65 (0.43-1.00)	0.049	15 (3.5)	0.77 (0.41-1.45)	0.42	55 (12.8)	0.86 (0.62-1.19)	0.36
Older (>50 y)									
Referent women	45 (14.0)	1.00 (reference)	—	17 (5.3)	1.00 (reference)	—	77 (24.0)	1.00 (reference)	—
Oophorectomy	29 (11.7)	0.80 (0.50-1.29)	0.36	12 (4.8)	0.94 (0.45-1.98)	0.87	48 (19.4)	0.80 (0.55-1.15)	0.22

[a]Cerebrovascular diseases include ischemic stroke (thrombotic, embolic, and lacunar infarcts) and hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage). Transient ischemic attacks and cerebrovascular events due to trauma, blood disorders, or malignancy were excluded.
[b]A sensitivity analysis excluding all women followed for less than 10 years yielded similar results (HR, 1.44; 95% CI, 0.96-2.17; $P = 0.08$).

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Third, it has been suggested that women who undergo hysterectomy have an adverse cardiovascular risk profile,[28] and almost all of the women in our study who underwent bilateral oophorectomy also had a hysterectomy (98%). Thus, bilateral oophorectomy could be associated with increased cardiovascular mortality because of its association with hysterectomy (confounding effect of hysterectomy). Unfortunately, we did not have information on cardiovascular risk factors at the time of oophorectomy. However, the association between bilateral oophorectomy and cardiovascular mortality remained similar when women who had a bilateral oophorectomy were compared with women who underwent hysterectomy (from the unilateral oophorectomy cohort). These findings suggest that the harmful effects of bilateral oophorectomy are not explained by hysterectomy and its associated risk profile. Our findings are also consistent with the recent findings from the Women's Health Initiative Coronary Artery Calcium Study.[12]

Fourth, information about estrogen use among the referent women was not abstracted. Thus, our analyses on the effect of estrogen treatment were restricted to women with bilateral oophorectomy. Interestingly, only 60% of the women who underwent bilateral oophorectomy were ever prescribed estrogen treatment.[19] Most women were treated with unopposed estrogen (conjugated equine estrogen therapy in 82% of the women).[19]

Fifth, the bilateral oophorectomies included in this cohort took place from 1950 through 1987. Thus, surgical practices and estrogen treatment may have differed from current clinical practice. However, sensitivity analyses stratified by index year showed that the association between oophorectomy before age 45 years and cardiovascular mortality was similar for the time periods 1950 through 1969 and 1970 through 1987 (data not shown). Sixth, it remains uncertain whether bilateral oophorectomy occurred before or after natural menopause in some of the 158 women who underwent the surgery before age 56 years. However, our significant findings were restricted to women with oophorectomy before age 45 years, and the occurrence of natural menopause before that age is rare. Seventh, the sample size and the corresponding statistical power were inadequate to consider some specific strata separately (eg, hemorrhagic stroke vs ischemic stroke). Similarly, the power was limited to study the modifying effect of estrogen treatment or to separate oral versus transdermal use of estrogen. Eighth, the population of Olmsted County is primarily white and of European ancestry; thus, our findings may not be generalizable to other populations with a different ethnic composition. Finally, there was some risk of false-positive findings because of multiple statistical testing.

Conclusions

This study showed that women who underwent early bilateral oophorectomy are at increased risk of death involving cardiovascular disease, especially cardiac diseases. However, treatment with estrogen through age 45 years or longer may reduce this risk. These findings, in conjunction with the results of other studies,[1,4,5,8] have important clinical implications and should prompt a reassessment of prophylactic bilateral oophorectomy in premenopausal women.[6,14]

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