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Research Article

Cancer Prevention Research

Bilateral Oophorectomy, Body Mass Index, and Mortality in U.S. Women Aged 40 Years and Older

Anne Marie McCarthy[1], Andy Menke[1], Pamela Ouyang[2], and Kala Visvanathan[1,3]

Abstract

Bilateral oophorectomy is used as a risk reduction strategy in *BRCA*1/2 mutation carriers, although data on long-term side effects are not yet available. In the general population, oophorectomy, particularly at a young age, has been associated with increased overall and cardiovascular disease (CVD) mortality. The mechanisms for this association are not well understood. We examined the association between prior bilateral oophorectomy, obesity, and all-cause, cancer, and CVD mortality. Our study population included women ages 40 and above from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative survey with enrollment from 1988 to 1994 and prospective mortality follow-up through December 31, 2006. We excluded women with a history of reproductive cancer or missing oophorectomy status, yielding a study population of 4,040. Cox proportional hazards modeling was used to estimate HR for all-cause and cause-specific mortality. In multivariate analyses, body mass index (BMI) significantly modified the association between oophorectomy and mortality ($P_{interaction}$ = 0.04). Women who were obese at the time of interview and who had an oophorectomy at less than 40 years were more than twice as likely to die [HR, 2.23; 95% confidence interval (CI), 1.25–3.98], particularly of CVD (HR, 2.77; 95% CI, 0.91–8.41), than nonobese women with intact ovaries. These associations persisted after excluding women who used estrogen therapy and women who had oophorectomy before 35 years of age. The joint effect of obesity and early oophorectomy on mortality was significantly greater than expected, given the independent effects of both exposures. Our results suggest that minimizing weight gain after oophorectomy and addressing cardiovascular risk factors could beneficially impact mortality. *Cancer Prev Res; 5(6); 847–54. ©2012 AACR.*

Introduction

Prophylactic salpingo-oophorectomy is recommended for women at high risk of ovarian cancer, such as *BRCA*1/2 mutation carriers, after child bearing, and/or after the age of 35 years to reduce cancer risk and prolong survival (1). The most comprehensive study among mutation carriers found that prophylactic oophorectomy was associated with significant reductions in all-cause, ovarian, and breast cancer mortality after a mean follow-up of approximately 6 years (2). It will be a number of years, however, before robust estimates of the long-term adverse effects of oophorectomy become available in *BRCA*1/2 mutation carriers given the recency of genetic testing. In the meantime, studies in the general population may provide data on how exposures such as obesity impact the long-term risk of death following oophorectomy. Oophorectomy before the age of 45 years has been associated with a modest increase in all-cause and cardiovascular disease (CVD) mortality (3–5), although the etiology has not been elucidated.

Animal studies have consistently shown a relationship between oophorectomy and an increase in adiposity (6–8) and metabolic perturbations such as insulin resistance (6, 9, 10), higher total and low-density lipoprotein (LDL) cholesterol (6, 11), chronic low-grade inflammation, and immune infiltration of adipocytes (7). These observations are supported by a limited number of clinical studies reporting higher blood levels of triglycerides, fasting glucose, insulin, LDL cholesterol, body mass index (BMI), and waist circumference among women who have undergone an oophorectomy than those with intact ovaries (12–15). Obesity has also been associated with increased CVD and cancer mortality (16). Collectively, these data suggest that adiposity may contribute to the increased mortality observed among young women who undergo oophorectomy (3–5). We examined this question using data from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample.

Authors' Affiliations: [1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; [2]Department of Medicine, Johns Hopkins University; and [3]Department of Medical Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland

Corresponding Author: Kala Visvanathan, Johns Hopkins, 615 N. Wolfe St., Baltimore, MD 21205. Phone: 410-614-1112; Fax: 410-614-2632; E-mail: kvisvana@jhsph.edu

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Methods

Study population

NHANES III was conducted from 1988 to 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. NHANES III is a nationally representative, cross-sectional, complex survey that included interviews, physical examinations, and blood testing. There were 10,649 female participants ages 17 and above. Details of the study have been previously published (17). NHANES III was approved by the NCHS Institutional Review Board, and informed consent was obtained from all participants.

The study population included women ages 40 and above who completed both the interview and exam (N = 5,076). Women were excluded if they did not answer the survey question about oophorectomy ($n = 324$), reported unilateral oophorectomy ($n = 361$) or unknown type of oophorectomy ($n = 9$), were missing age at oophorectomy ($n = 13$), reported hysterectomy at a younger age than oophorectomy ($n = 43$), were pregnant ($n = 5$), missing BMI ($n = 20$), missing mortality status ($n = 2$), or reported a prior reproductive cancer (breast, $n = 94$; cervical, $n = 27$; uterine, $n = 39$; and ovarian, $n = 11$). Women who were underweight (ref. 18; BMI < 18.5 kg/m^2, $n = 88$) were also excluded as they have higher mortality rate than normal weight women in NHANES studies (19). This resulted in an analytic population of 4,040. For brevity, "oophorectomy" will denote "bilateral oophorectomy" in the rest of the manuscript.

Covariates

Information was available on prior gynecologic surgery and use of oral estrogen therapy or female hormone pills. Detailed information about type of hormone replacement therapy (HRT) was not ascertained. We categorized menopausal status at interview in the following manner: premenopausal women reported a menstrual period or pregnancy in the last year and postmenopausal women reported bilateral oophorectomy or no menstrual period in the last year. Women who reported hysterectomy, used HRT or birth control in the last year, or were missing data on relevant questions were categorized separately as these factors could affect report of menstrual bleeding. For this subgroup ($n = 483$), women younger than 51 years were categorized as premenopausal and women older than 51 years were considered postmenopausal, based on the average age at menopause in the U.S. (20). Information on menopause status just before oophorectomy was not collected. Survey staff conducted standardized measurements of weight and height, and BMI was calculated [weight (kg)/height (m)^2] and categorized: 18.5–24.9 kg/m^2 (normal, reference group), 25.0–29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese; ref. 21). BMI at the age of 25 years was calculated from self-reported weight at age 25 and height at interview. Smoking was categorized as never (<100 cigarettes), former (100+ cigarettes, not currently smoking), or current.

Mortality follow-up

NHANES III participants ages 17 and above were linked to the National Death Index (NDI). A complete description of the linkage methodology can be found online (22).

Person-years of follow-up were calculated from the date of examination until date of death or censoring on December 31, 2006. Cause of death was determined using underlying cause of death codes from death certificates. Deaths occurring before 1999 were re-coded to correspond to ICD-10 codes by NCHS (23). ICD-10 codes C00-C97 were categorized cancer deaths and ICD-10 codes I00-I78 were categorized as CVD deaths. For cause-specific mortality analyses, women who died of other causes were censored.

Statistical analysis

All analyses incorporated examination sampling weights using survey commands in Stata IC 10 and SUDAAN 10.0. All-cause and cause-specific mortality rates were calculated by oophorectomy status and age-standardized to the 2000 Census Population using the direct method with 5-year age intervals. Weighted means and proportions of descriptive statistics were calculated by oophorectomy status and P values were derived from Pearson χ^2 or Wald tests. Cox proportional hazards regression was used to evaluate the association between oophorectomy and all-cause, cancer, and CVD mortality. Oophorectomy status was categorized no oophorectomy (reference group), oophorectomy <40 years, and oophorectomy ≥40 years based on our clinical question (24). Also, the majority of women were likely to be premenopausal at the age of 40. The proportional hazards assumption was tested using Schoenfeld residuals, and there were no significant departures from proportionality. Multivariate models were adjusted for age at interview, race, income, education, alcohol use, and smoking. BMI at interview was included in the model to assess its role as a mediator of the association between oophorectomy and mortality. The independent and joint effects of BMI and oophorectomy on mortality were also evaluated. Interactions between oophorectomy status and obesity were tested by introducing cross-product terms in multivariate models with the Wald test of statistical significance.

Self-reported weight at the age of 25 was ascertained, but frequently missing ($n = 406$) and therefore was not adjusted for in the main analysis. Rather, we conducted a sensitivity analysis among women who reported their weight at the age of 25 and excluding women with oophorectomy conducted younger than 25 years. Additional sensitivity analyses were conducted excluding hormone users and examining various cutoff points for age at oophorectomy based on the published literature (3, 5). In addition, we conducted separate analyses restricted to specific groups as outlined in the results. Finally, we limited the analysis to women who reported hysterectomy, comparing women with oophorectomy and hysterectomy to women with hysterectomy alone.

Results

Table 1 compares descriptive characteristics for 575 women ages 40 years and above at interview who reported an

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Table 1. Characteristics of women 40 years and older in NHANES III 1988–1994, N = 4,040

Characteristics	Prior oophorectomy (N = 575)	Intact ovaries (N = 3,465)	*P*
Age at interview, mean (SD), y	61.1 (11.8)	57.3 (13.2)	<0.001
Age at oophorectomy, median (range), y	43 (19–79)	—	
Race, %			0.01
Non-Hispanic white	85.1	79.5	
Non-Hispanic black	10.0	9.5	
Mexican-American	2.0	3.7	
Other	3.0	7.4	
Income, %			0.02
<$20,000	41.3	34.5	
≥$20,000	57.5	63.3	
Missing	1.2	2.2	
Education, %			0.003
<12 y	33.4	27.0	
12 y	38.3	35.8	
>12 y	27.9	36.7	
Region, %			0.01
Northeast	20.0	21.2	
Midwest	21.3	24.3	
South	40.4	32.0	
West	18.3	22.6	
Parity, %			0.03
≥2	67.8	75.5	
1	16.1	12.0	
Nulliparous	16.1	12.5	
Ever used birth control, %	35.0	46.9	<0.001
Hysterectomy, %	98.4	14.9	<0.001
Ever used estrogen pills	67.3	18.2	<0.001
Current use	39.3	7.4	
Former use	27.9	10.8	
Postmenopausal	100.0	58.8	<0.001
Alcohol use, ≥12 drinks past year, %	27.6	37.5	0.002
Smoking, %			0.97
Never	56.1	56.0	
Former	25.4	25.9	
Current	18.5	18.1	
BMI, mean (SD), kg/m^2	28.0 (6.4)	27.5 (6.1)	0.17
Weight at age 25, mean (SD), lbs	126.9 (22.4)	126.7 (22.9)	0.92

oophorectomy and 3,465 women with intact ovaries. The median age at oophorectomy was 43 years, and the median time since oophorectomy was 18 years. Women with oophorectomy were older, less educated, had lower income, were more likely to reside in the South, and drank less alcohol than women with intact ovaries. Mean BMI at interview did not differ significantly by oophorectomy status ($P = 0.17$), nor did self-reported weight at the age of 25 years ($P = 0.92$). Women who had an oophorectomy were more likely to report CVD (heart attack, congestive heart failure, stroke) after the procedure than women with intact ovaries (data not shown, 11.0% vs. 7.1%; $P = 0.015$). There were 1,362 total deaths, 631 CVD deaths, and 267 cancer deaths, with a median follow-up of 14.3 years since interview. The most common cancer deaths were lung ($N = 74$), breast ($N = 32$), and colorectal cancer ($N = 25$), and their frequency was similar by oophorectomy status. Women with oophorectomy had higher all-cause and CVD mortality rates than women with intact ovaries (Fig. 1).

Table 2 displays the HRs for all-cause, cancer, and CVD mortality by categories of BMI and by oophorectomy status. In multivariate models, adjusting for age at interview, race, income, education, smoking, and alcohol, obesity (BMI ≥ 30 kg/m^2) was associated with increased all-cause mortality [HR, 1.37; 95% confidence interval (CI), 1.19–1.59] as well as both cancer-specific (HR, 1.44; 95% CI, 0.98–2.12) and CVD mortality (HR, 1.35; 95% CI, 1.00–1.83).

Overall, oophorectomy was not significantly associated with all-cause, cancer, or CVD mortality in either age-adjusted or multivariate models when compared with

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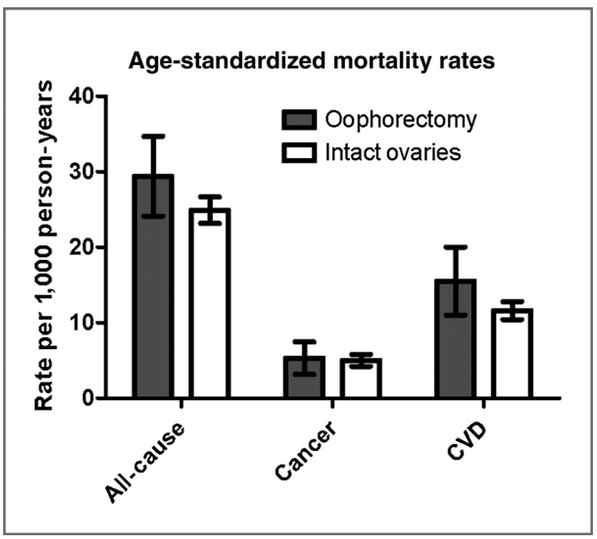

Figure 1. All-cause, cancer, and CVD mortality rates per 1,000 person-years of follow-up, NHANES III 1988–1994. Age standardized to the 2000 U.S. Census Population using the direct method with 5-year age intervals. Error bars represent 95% confidence intervals.

women with intact ovaries. However, in women who had an oophorectomy before the age of 40, a 48% increase in all-cause mortality was observed in age-adjusted models (HR, 1.48; 95% CI, 1.03–2.13). In multivariate models adjusted for age at interview, race, income, education, smoking, alcohol, and BMI at interview, the HR for all-cause mortality was increased for women with oophorectomy younger than 40 years, but it was not statistically significant (HR, 1.35; 95% CI, 0.93–1.99).

Table 3 reports the joint effect of BMI at interview and oophorectomy. Obese women who reported an oophorectomy had nearly 2-fold higher all-cause mortality than women with normal BMI and intact ovaries (HR, 1.94; 95% CI, 1.35–2.77). Of note, this point estimate for all-cause mortality in obese women with an oophorectomy was higher than that observed for obese women with intact ovaries (HR, 1.33; 95% CI, 1.12–1.57). Similar findings were observed for CVD mortality (HR, 1.84; 95% CI, 0.99–3.43). To better test for interactions between BMI and age at oophorectomy with respect to mortality, we collapsed BMI categories with similar HRs. The risk of death continued to increase for obese women with oophorectomy compared

Table 2. All-cause, cancer, and CVD mortality by bilateral oophorectomy and age at bilateral oophorectomy, NHANES III 1988–1994 (N = 4,040)

			All-cause mortality (N = 1,362 deaths)		Cancer mortality (N = 267 deaths)		CVD mortality (N = 631 deaths)	
	N	Person-years	Died (N)	HR (95% CI)	Died (N)	HR (95% CI)	Died (N)	HR (95% CI)
Age-adjusted[a]								
BMI, kg/m^2								
<25	1,293	16,164	447	1.00 (reference)	94	1.00 (reference)	209	1.00 (reference)
25–29.9	1,391	17,514	502	1.08 (0.92–1.27)	82	1.02 (0.71–1.46)	237	1.05 (0.84–1.30)
30+	1,356	17,450	413	1.38 (1.21–1.58)[c]	91	1.35 (0.92–1.98)	185	1.41 (1.06–1.86)[c]
Multivariate[b]								
BMI, kg/m^2								
<25	1,293	16,164	447	1.00 (reference)	94	1.00 (reference)	209	1.00 (reference)
25–29.9	1,391	17,514	502	1.10 (0.93–1.30)	82	1.12 (0.78–1.61)	237	1.04 (0.85–1.29)
30+	1,356	17,450	413	1.37 (1.19–1.59)[c]	91	1.44 (0.98–2.12)	185	1.35 (1.00–1.83)
Age-adjusted[a]								
Ooph								
No ooph	3,465	43,968	1,152	1.00 (reference)	228	1.00 (reference)	529	1.00 (reference)
Total ooph	575	7,160	210	1.13 (0.87–1.46)	39	1.12 (0.74–1.70)	102	1.21 (0.87–1.70)
Age at ooph < 40	205	2,624	72	1.48 (1.03–2.13)	12	1.37 (0.68–2.79)	35	1.66 (0.94–2.93)
Age at ooph ≥ 40	370	4,536	138	0.98 (0.71–1.34)	27	1.00 (0.58–1.73)	67	1.03 (0.73–1.45)
Multivariate[b]								
Ooph								
No ooph	3,465	43,968	1,152	1.00 (reference)	228	1.00 (reference)	529	1.00 (reference)
Total ooph	575	7,160	210	1.14 (0.88–1.46)	39	1.10 (0.73–1.66)	102	1.22 (0.86–1.73)
Age at ooph < 40	205	2,624	72	1.35 (0.93–1.99)	12	1.20 (0.60–2.39)	35	1.56 (0.85–2.86)
Age at ooph ≥ 40	370	4,536	138	1.03 (0.79–1.35)	27	1.05 (0.62–1.76)	67	1.06 (0.75–1.49)

Abbreviation: Ooph, oophorectomy.

[a]Separate Cox proportional hazards models for BMI at interview and oophorectomy status, each adjusted for age at interview.

[b]Cox proportional hazards model includes both BMI at interview and oophorectomy status, adjusted for age at interview, race/ethnicity, income, smoking, education, and current alcohol use.

[c]$P_{trend} < 0.05$.

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Table 3. Joint effects of BMI and oophorectomy on all-cause, cancer, and CVD mortality, NHANES III 1988–1994 (N = 4,040)

			All-cause mortality (N = 1,362 deaths)		Cancer mortality (N = 267 deaths)		CVD mortality (N = 631 deaths)	
	N	Person-years	Died (N)	HR (95% CI)	Died (N)	HR (95% CI)	Died (N)	HR (95% CI)
Model 1[a]								
BMI < 25 and no ooph	1,115	13,974	376	1.00 (reference)	79	1.00 (reference)	177	1.00 (reference)
BMI < 25 and ooph	178	2,190	71	1.26 (0.91–1.76)	15	1.47 (0.72–3.04)	32	1.26 (0.82–1.93)
BMI 25–29.9 and no ooph	1,190	14,973	437	1.19 (0.99–1.43)	70	1.26 (0.84–1.90)	201	1.08 (0.84–1.37)
BMI 25–29.9 and ooph	201	2,540	65	0.93 (0.68–1.27)	12	0.95 (0.41–2.19)	36	1.12 (0.73–1.72)
BMI 30+ and no ooph	1,160	15,020	339	1.33 (1.12–1.57)	79	1.54 (1.04–2.27)	151	1.32 (0.96–1.82)
BMI 30+ and ooph	196	2,430	74	1.94 (1.35–2.77)	12	1.63 (0.85–3.12)	34	1.84 (0.99–3.43)
$P_{interaction}$				0.57		0.47		0.79
Model 2[a]								
No ooph and BMI < 30	2,305	28,948	813	1.00 (reference)	149	1.00 (reference)	378	1.00 (reference)
Ooph < 40 and BMI < 30	122	1,572	45	1.18 (0.81–1.71)	9	1.26 (0.55–2.89)	21	1.33 (0.81–2.19)
Ooph ≥ 40 and BMI < 30	257	3,159	91	0.93 (0.70–1.23)	18	1.03 (0.51–2.08)	47	1.06 (0.76–1.49)
No ooph and BMI ≥ 30	1,160	15,020	339	1.22 (1.05–1.41)	79	1.38 (1.01–1.89)	151	1.27 (0.93–1.74)
Ooph < 40 and BMI ≥ 30	83	1,053	27	2.23 (1.25–3.98)	3	1.46 (0.35–6.14)	14	2.77 (0.91–8.41)
Ooph ≥ 40 and BMI ≥ 30	113	1,377	47	1.56 (1.06–2.31)	9	1.45 (0.69–3.00)	20	1.34 (0.77–2.32)
$P_{interaction}$				0.04		0.95		0.67
Model 3: HRT never users (N = 3,137)[a,b]								
No ooph and BMI < 30	1,912	23,847	695	1.00 (reference)	117	1.00 (reference)	326	1.00 (reference)
Ooph < 40 and BMI < 30	44	549	18	0.78 (0.46–1.33)	2	0.32 (0.06–1.77)	12	1.38 (0.76–2.52)
Ooph ≥ 40 and BMI < 30	91	1,025	47	1.01 (0.66–1.55)	7	0.69 (0.29–1.67)	27	1.41 (0.77–2.58)
No ooph and BMI ≥ 30	1,002	12,986	289	1.09 (0.93–1.29)	66	1.39 (0.95–2.05)	128	1.09 (0.80–1.50)
Ooph < 40 and BMI ≥ 30	33	395	14	2.81 (1.47–5.37)	2	2.77 (0.37–20.6)	7	2.80 (0.59–13.2)
Ooph ≥ 40 and BMI ≥ 30	55	637	29	1.53 (1.03–2.27)	6	1.84 (0.69–4.87)	14	1.29 (0.65–2.56)
$P_{interaction}$				0.02		0.24		0.99

Abbreviation: Ooph, oophorectomy.

[a]Cox proportional hazards model adjusted for age at interview, race/ethnicity, income, smoking, education and current alcohol use.

[b]Excludes women who reported ever using estrogen pills.

with nonobese women with intact ovaries (HR, 1.76; 95% CI, 1.23–2.51; data not shown). The risk was greatest among obese women who had an oophorectomy before the age of 40 (Table 3, model 2, and Fig. 2; HR, 2.23; 95% CI, 1.25–3.98). The risk was smaller but still elevated in obese women who had an oophorectomy at 40 years or above (HR, 1.56; 95% CI, 1.06–2.31) compared with nonobese women with intact ovaries. Furthermore, the interaction between obesity and age at oophorectomy for all-cause mortality was statistically significant ($P_{interaction} = 0.04$). A similar pattern was observed for CVD mortality, although the interactions were not statistically significant.

The interaction between BMI and age at oophorectomy for all-cause mortality was still observed after excluding current or former HRT users (Table 3, model 3, $P_{interaction} = 0.02$). Among HRT nonusers, obese women who reported oophorectomy at less than 40 years were nearly 3 times more likely to die than nonobese women with intact ovaries (HR, 2.81; 95% CI, 1.47–5.37). Sensitivity analyses adjusting for BMI at age 25, limiting the control group to postmenopausal women, excluding women older than 70 at interview, limiting to women with oophorectomy within the past 10 or 15 years, and excluding women who died within 1 or 5 years of interview yielded similar results as the complete analysis. We examined the effect of different cutoff points for age at oophorectomy and found the strongest effect in women whose oophorectomy was conducted before the age of 40 years, even when women with oophorectomy conducted before the age of 35 years were excluded. Excluding women who reported a history of CVD or nonskin cancer at baseline did not alter the results significantly. Finally, results were also similar after restricting to women who reported hysterectomy (data not shown).

Discussion

To our knowledge, this is the first population-based study to establish a link between oophorectomy, adiposity, and mortality. We identified a subgroup of women who were at a greater risk of death following oophorectomy. Obese women who underwent oophorectomy before the age of 40 years had nearly 2-fold increased mortality, primarily

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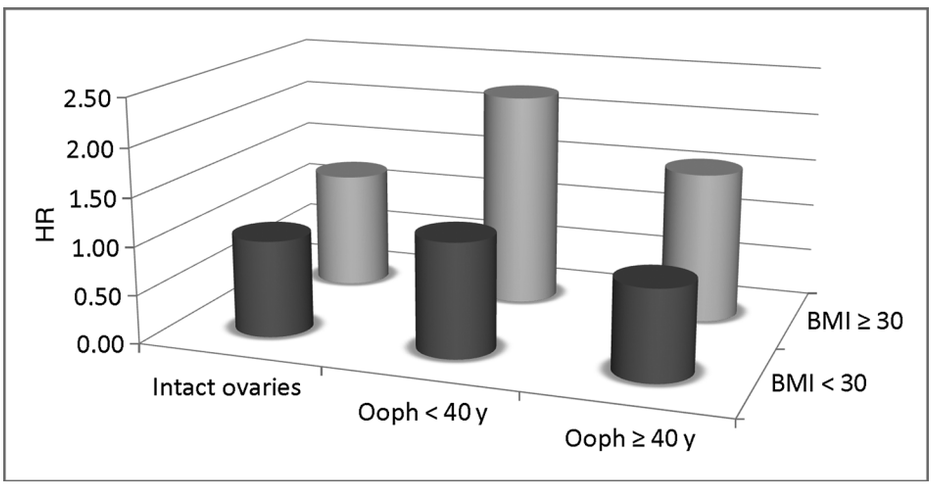

Figure 2. Joint effects of age at oophorectomy and obesity on all-cause mortality, NHANES III 1988–1994. Cox proportional hazards model adjusted for age at interview, race/ethnicity, income, smoking, education, and current alcohol use. Ooph, bilateral oophorectomy; BMI, body mass index kg/m^2; HR, hazard ratio.

due to CVD, compared with nonobese women with intact ovaries. The magnitude of this effect was greater than that expected, given the independent effects of both obesity and oophorectomy on mortality. Furthermore, among women who did not report use of HRT, obese women who had an oophorectomy before the age of 40 years were nearly 3 times more likely to die than nonobese women with intact ovaries. This relationship persisted after excluding those with oophorectomy conducted before the age of 35 years.

A few population-based, cross-sectional studies have shown an association between oophorectomy and adiposity. A study of 1,052 women ages 40 to 69 years in Norway reported that women post-oophorectomy were more likely to have BMI $\geq$30 kg/m^2 and a waist circumference greater than 88 cm compared with age-matched controls with intact ovaries (15), whereas a survey of 1,150 postmenopausal women ages 50 to 89 years in the United States found no differences in BMI or waist-to-hip ratio between women with oophorectomy and those with intact ovaries (12). In animal models, oophorectomy has consistently been shown to increase adiposity, in conjunction with insulin resistance, inflammation, and increased adipokine levels (6–7, 11). In addition, behavioral and psychosocial factors such as reduced physical activity and a leptin-mediated increase in appetite may also play a role (7, 11, 25, 26).

While women who underwent oophorectomy, particularly at young age, had increased all-cause and CVD mortality, this did not reach statistical significance in multivariate analyses. However, our findings are consistent with prior studies which have reported between 18% and 67% increases in all-cause and CVD mortality for women with oophorectomy compared with women with intact ovaries irrespective of hysterectomy status, particularly among women who underwent removal of the ovaries before the age of 45 years (3–5). Previous studies also found higher mortality risk in nonestrogen users (3–5), suggesting that estrogen use may be beneficial. A Dutch study showed that later age at oophorectomy was associated with lower total and CVD mortality after a mean of 17 years of follow-up (27). Furthermore, a recent analysis of the Women's Health Initiative observational study found no significant increases in CVD events or mortality when comparing women with oophorectomy and hysterectomy with women with hysterectomy alone (28), although the HRs for fatal and nonfatal CVD were elevated (HR, 1.33) in women younger than 50 years who never used HRT. Several studies and a meta-analysis also support a positive association between oophorectomy and CVD incidence (27, 29–31). However, the association between oophorectomy, adiposity, and mortality has not been examined in these studies or others, although a few studies adjusted for BMI (5, 27, 28, 30, 31).

We were not able to directly examine the effect of HRT use, as NHANES III did not ascertain information on the type of HRT used. In addition, the appropriate comparison group for women with oophorectomy who used HRT would be women who had hysterectomy alone and used HRT, as both groups of women would likely be prescribed estrogen-only therapy. However, there were too few women in the hysterectomy-only group to make meaningful comparisons among HRT users. However, the fact that risk estimates were similar or increased after excluding HRT users further supports our findings as HRT use may mask the independent effect of oophorectomy on adiposity. A limitation of our study is the inability to determine the temporality of the association between oophorectomy and adiposity, as BMI at the time of surgery is unavailable. However, women with oophorectomy reported similar BMI at the age of 25 years as women with intact ovaries, and results were similar after adjustment for BMI at the age of 25 years.

We cannot rule out the possibility that increased CVD mortality among women with oophorectomy may be related to confounding by indication for surgery. Underlying conditions that result in gynecologic surgery, such as uterine fibroids or endometriosis, may predispose women to developing cardiovascular complications, or women with these conditions may have more heart disease risk factors. However, studies stratified by indication for oophorectomy found similar mortality rates among women whose indication for surgery was prophylactic versus benign conditions (3, 4).

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Strengths of the study include the use of a large, nationally representative sample with nearly 600 women who underwent oophorectomy, and more than 200 had surgery before the age of 40 years. To our knowledge, this is the first study to assess the joint effect of oophorectomy and high BMI on long-term mortality risk. Previous studies have lacked data on BMI (3, 4) or have merely adjusted for it (5). NHANES III staff conducted standardized body measurements, increasing accuracy of BMI measures compared with studies using self-reported BMI. In addition, NHANES III included information on a variety of demographic and lifestyle factors, as well as 12 to 18 years of prospective mortality follow-up.

Several limitations should be considered when interpreting our findings. Self-report of oophorectomy has not been validated in NHANES III, however based on previous validation studies, we do not expect significant differential misclassification by mortality status (32–34). There were few cancer deaths in this cohort, yielding limited power to detect differences in cancer mortality by oophorectomy status. However, it was reassuring that we did not see large differences in specific cancers. Women were enrolled at an average of 18.5 years following oophorectomy. Therefore, women who underwent oophorectomy and developed CVD early may be less likely to participate or may have died before being enrolled in the study. However, if this was the case, the "true" association between oophorectomy and CVD may be stronger than what we reported.

In conclusion, the results of our study suggest that the combined effect of obesity and bilateral oophorectomy is associated with increased mortality, particularly due to CVD, compared with their independent effects. Our novel results suggest that young women undergoing oophorectomy should be monitored long-term for weight gain and CVD risk factors. This is important information for high-risk women considering early oophorectomy for cancer risk reduction and their physicians, as it can help minimize adverse effects associated with this procedure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were declared.

Authors' Contributions

Conception and design: A.M. McCarthy, K. Visvanathan
Development of methodology: A.M. McCarthy, K. Visvanathan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. McCarthy,
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. McCarthy, A. Menke, K. Visvanathan
Writing, review, and/or revision of the manuscript: A.M. McCarthy, A. Menke, P. Ouyang, K. Visvanathan
Study supervision: K. Visvanathan

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