Published in final edited form as:
Obstet Gynecol. 2009 May ; 113(5): 1027–1037. doi:10.1097/AOG.0b013e3181a11c64.

Ovarian Conservation at the Time of Hysterectomy and Long-Term Health Outcomes in the Nurses' Health Study

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Abstract

Objective—To report long-term health outcomes and mortality after oophorectomy or ovarian conservation.

Methods—We conducted a prospective, observational study of 29,380 women participants of the Nurses' Health Study who had a hysterectomy for benign disease; 16,345 (55.6%) had hysterectomy with bilateral oophorectomy and 13,035 (44.4%) had hysterectomy with ovarian conservation. We evaluated incident events or death due to coronary heart disease (CHD), stroke, breast cancer, ovarian cancer, lung cancer, colorectal cancer, total cancers, hip fracture, pulmonary embolus, and death from all causes.

Results—Over 24 years of follow-up, for women with hysterectomy and bilateral oophorectomy, compared with ovarian conservation, the multivariable hazard ratios (HR) were 1.12 (95% CI 1.03, 1.21) for total mortality, 1.17 (95% CI 1.02, 1.35) for fatal plus nonfatal CHD, and 1.14 (95% CI 0.98, 1.33) for stroke. Although the risks of breast (HR 0.75 95% CI 0.68, 0.84), ovarian (HR 0.04 95% CI 0.01, 0.09, NNT = 220), and total cancers (HR 0.92 95% CI 0.86, 0.98) decreased after oophorectomy, lung cancer incidence (HR =1.26, 95% CI 1.02, 1.56, NNH = 190) and total cancer mortality (HR=1.17, 95% CI 1.04, 1.32) increased. For never-users of estrogen therapy, bilateral oophorectomy before age 50 was associated with an increased risk of all-cause

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Financial Disclosure: Dr. Parker has been a consultant to Ethicon Women's Health (Cincinatti, OH). Dr. Broder is president of Partnership for Health Analytic Research (Los Angeles, CA). Dr. Chang is an employee of Partnership for Health Analytic Research. Dr. Farquhar has received consulting fees from the World Health Organization (Geneva, Switzerland). Dr. Shoupe has received a research grant from the NIH National Center of Complementary and Alternative Medicine (Gaithersburg, MD). Drs. Liu, Manson, Feskanich, Berek, and Manson did not report any potential conflicts of interest.

mortality, CHD, and stroke. With an approximate 35-year life span following surgery, one additional death would be expected for every 9 oophorectomies performed.

Conclusions—Compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy for benign disease is associated with a decreased risk of breast and ovarian cancer, but an increased risk of all-cause mortality, fatal and non-fatal coronary heart disease, and lung cancer. In no analysis or age-group was oophorectomy associated with increased survival.

Introduction

Bilateral oophorectomy at the time of hysterectomy for benign disease is commonly practiced in order to prevent subsequent development of ovarian cancer.(1) Data from the CDC show that for women having a hysterectomy between ages 40-44, 50% have concurrent oophorectomy and between ages 45-64, 78% have oophorectomy.(2) In all, approximately 300,000 U.S. women have a prophylactic oophorectomy every year.

Oophorectomy before menopause leads to an abrupt reduction in endogenous estrogen and androgen production.(3) Postmenopausal ovaries continue to produce significant amounts of testosterone and androstenedione which are converted to estrogen peripherally.(4,5) Later age of menopause has been associated with a reduced risk of death from coronary heart disease and stroke and studies show that preserving ovarian function is associated with a lower risk of coronary heart disease.(6,7,8,9) Among US women, ovarian cancer accounts for 14,700 deaths per year, whereas coronary heart disease accounts for 326,900 deaths and stroke for approximately 86,900 deaths each year.(10)

Ovarian conservation, therefore, might benefit overall survival in women not at high risk for ovarian cancer.(11) The objective of this study was to report long-term health outcomes and mortality after ovarian conservation or oophorectomy.

Materials and Methods

Study Population

We used the database from the Nurses' Health Study (NHS) cohort, which included 122,700 married registered nurses who were ages 30 to 55 in 1976 when the initial questionnaires were mailed. Race was self-reported and the cohort was 94% white, 2% African-American, 1% Asian, 1% multi-racial and 2% other. The cohort was relatively homogeneous with regard to education, socioeconomic status and access to health-care. (12) Additional questionnaires, updating risk-factors and newly diagnosed health conditions have been sent every two years with response rates of approximately 90% for each cycle. In this cohort, a validation study found self-reported oophorectomy at the time of hysterectomy to be very accurate when compared with medical records.(13) NHS participants with a previous hysterectomy entered study follow-up in 1980. Others entered when they reported having a hysterectomy on the 1982 through 2002 questionnaires.

All eligible NHS participants were initially included prior to application of exclusion criteria. Through 2002, 50,432 NHS participants reported having a hysterectomy without a diagnosis of gynecologic cancer. Women were excluded from this study if they had unilateral or partial oophorectomy (n=4,817), unknown ovarian status at the time of hysterectomy (n=2,559), a prior history of an outcome of interest as described below (n=8,525) or an oophorectomy (n=465) prior to their hysterectomy, or an unknown age at hysterectomy (n=4,643). Women with missing information on past oral contraceptive use were excluded due to the small number in this category (n=43). The remaining 29,380 women were included in the analysis; 16,345 (55.6%) had a hysterectomy with bilateral

oophorectomy and 13,035 (44.4%) had hysterectomy with ovarian conservation. Submission of a completed self-administered questionnaire was deemed to imply informed consent. The institutional review boards at John Wayne Cancer Institute at Saint John's Health Center in Los Angeles and Brigham and Women's Hospital in Boston approved this study.

Study Variables

Outcomes of Interest—We focused on incident events and death due to the following conditions: coronary heart disease (ICD-8:410—414), stroke (ICD-8:430—438), breast cancer (ICD-8:174), epithelial ovarian cancer (ICD-8:183), lung cancer (ICD-8:162), colorectal cancer, (ICD-8:153, 154), hip fracture (ICD-9:820.3), pulmonary embolus (ICD-8:450) and death due to all-causes. Hip fracture was confirmed by self-report alone; ovarian cancer was confirmed by medical record review, and all other events were confirmed either by medical record or by the participant in writing or by telephone interview.(13) If a diagnosis could not be confirmed or rejected, the event was excluded and the follow-up period was censored thereafter. Cause of death was determined using death certificates, autopsy reports and medical records. Mortality follow-up using the National Death Index and next of kin was more than 98% complete.(14)

Other Variables—Participant's age in months and biennial questionnaire cycle were used as stratification variables in the Cox proportional hazards models. For each outcome analysis, we adjusted for related risk factors: age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, tubal ligation, family history of breast cancer, family history of ovarian cancer, body mass index (BMI), smoking status, use of estrogen therapy (ET), duration of oral contraceptive (OC) use, alcohol consumption, physical activity and ASA use (Table 1). Alcohol consumption, physical activity, and use of ASA were initially queried in 1980. All data were updated at biennial questionnaire cycles. Family history of ovarian cancer (mother or sister) was first asked in 1992 and, once reported, was not updated. For all variables, missing information was separately noted.

Statistical Analysis

Women contributed person-time from the return of the 1980 questionnaire or the questionnaire on which they first reported having a hysterectomy until report of an outcome of interest, oophorectomy subsequent to hysterectomy, death, or end of follow-up on June 1, 2004. In analyses of incident events, women were censored only upon report of the event under analysis, therefore the numbers of person-years varied for each outcome. We calculated incidence rates by dividing the number of incident cases by the total number of person-years for simple hysterectomy or hysterectomy with bilateral oophorectomy. For multivariable analyses, we used Cox proportional hazards models to estimate relative risk (RR) and corresponding 95% confidence intervals (95% CI). Age and questionnaire cycle were stratifying variables in the analyses and were controlled for multiple potential confounders, as described in Table 1 and listed in the footnotes of each table.

The study design stratified the cohort into three sub-cohorts based on age at hysterectomy: <45, 45-54 and ≥55 and we conducted modeling separately for each. In a secondary analysis of oophorectomy status among never-users of estrogen therapy, women were stratified into two age groups (<50, ≥50) to gain statistical power and all analyses were repeated. All data transformations and statistical analyses were performed using SAS© version 9.1. (SAS Institute, Cary, NC) All P values were based on two-sided tests with significance of 0.05.

RESULTS

Women with ovarian conservation and those with bilateral oophorectomy had similar baseline distributions of risk factors for cardiovascular disease and cancer, but the latter were slightly older and more likely to be current or past users of hormone therapy (Table 1). After adjustment for multiple relevant risk-factors, we compared the two groups in relation to the incidence of fatal and non-fatal events during 24 years of follow-up (Table 2 – cancer events, Table 3 – non-cancer events, Table 4 - **deaths**). Oophorectomy was associated with an increased risk of coronary heart disease; this increase was statistically significant for all women (HR 1.17 95% CI 1.02, 1.35), and for women having oophorectomy before age 45 (HR 1.26 95% CI 1.04, 1.54). Breast cancer was less frequent among all women having oophorectomy (HR 0.75 95% CI 0.68, 0.84), and the risk was lower among women having oophorectomy before the age of 45 (HR 0.62 95% CI 0.53, 0.74). Oophorectomy was associated with a markedly reduced risk of ovarian cancer (HR 0.04; 95% CI, 0.01-0.09), an increased risk of lung cancer (HR 1.26; 95% CI, 1.02-1.56), and a reduction in total cancers (HR 0.92 95% CI 0.86, 0.98). Risks of stroke, hip fracture, colorectal cancer and pulmonary embolism did not differ significantly between groups. We documented 3,197 deaths from any cause; 350 women (10.9%) died from coronary heart disease, 219 (6.9%) from stroke, 230 (7.2%) from breast cancer, 37 (1.2%) from ovarian cancer, 336 (10.5%) from lung cancer, 118 (3.7%) from colorectal cancer, none due to hip fracture, 12 (0.4%) from pulmonary embolism and 1895 (59.3%) from other causes.

Among women having a simple hysterectomy, 1242 died (527 per 100,000 person-years) and among women having a hysterectomy with bilateral oophorectomy 1955 died (648 per 100,000 person-years). In multivariable analysis, oophorectomy increased the risk of death from any cause (HR 1.12 95% CI 1.03, 1.21). For every 24 women having bilateral oophorectomy, at least one women will die prematurely from any cause as a result of the oophorectomy. Analysis of cause-specific mortality found an increased risk of death from CHD (HR 1.28 95% CI 1.00, 1.64), lung cancer (HR 1.31 95% CI 1.02, 1.68), and all cancers (HR 1.17, 95% CI 1.04, 1.32), a reduced risk of death from ovarian cancer (HR 0.06; 95% CI, 0.02-0.21), and no overall difference in deaths from stroke, breast cancer, or colorectal cancer. For every 130 women having bilateral oophorectomy, one extra death from CHD will occur as a result of the oophorectomy. Analysis of death from pulmonary embolism was precluded by the small numbers of deaths.

Secondary Analyses

We performed an analysis of the 10,094 women who had either bilateral oophorectomy or ovarian conservation and had never used estrogen therapy (ET), stratified by age at hysterectomy <50 and ≥50 years. Never-users of ET who had oophorectomy before age 50 had a higher risk of incident coronary heart disease (HR 1.98 95% CI 1.18, 3.32). Oophorectomy was associated with a significantly increased risk of stroke for all women (HR 1.85 95% CI 1.09, 3.16) and for women younger than 50 at the time of surgery (HR 2.19 95% CI 1.16, 4.14). Oophorectomy was associated with an increased the risk of lung cancer (HR 2.09 95% 1.01, 4.33). The risk of all-cause death was significantly higher among women younger than 50 at the time of surgery (HR 1.40 95% CI 1.01, 1.96). The risks of breast cancer, colorectal cancer, total cancer, hip fracture and pulmonary embolus were no different among women who had never used ET.

DISCUSSION

This large prospective study of women having a hysterectomy for benign disease indicates that concurrent bilateral oophorectomy, after adjustment for multiple independent risk factors, is associated with a higher risk of all-cause mortality, primarily from coronary heart

disease and lung cancer, when compared with ovarian conservation. Furthermore, prophylactic oophorectomy did not improve survival at any age. During 24 years of follow-up, among 13,305 women who had ovarian conservation, 34 (0.26%) died from ovarian cancer. We did not find increased risks for colorectal cancer, pulmonary embolus or hip fracture in any analysis. Whereas breast cancer, ovarian cancer and all cancers were less frequent, the overall risk of death from cancer was greater among women having oophorectomy. The basis for this paradox is unclear and warrants further study. In a secondary analysis of women who never used estrogen therapy, oophorectomy was associated with an increased risk for incident stroke and lung cancer, and oophorectomy before age 50 was associated with an increased risk of fatal plus nonfatal coronary heart disease, stroke, and deaths from all causes. Total cancer risk was neither increased nor decreased among women with oophorectomy who had never used ET.

Our study has several strengths. This is the largest prospective study, with the longest follow-up, to examine the effect of oophorectomy on health outcomes in women. Although our study is observational, the NHS cohort is particularly homogenous relative to a study in the general population, with regards to educational and socioeconomic factors that may possibly confound non-randomized studies. In order to reduce the possibility of confounding due to the indication for surgery, women with any prior diagnosis of cancer or prior unilateral oophorectomy were excluded from our analysis. In order to reduce the possibility of confounding due to the family history, our main analysis was adjusted for both family history of breast or ovarian cancer. We also performed a subset analysis that excluded women with a family history of ovarian cancer (approximately 4.5% of study subjects) and found results similar to those presented in our manuscript (data not shown).

Many previous studies were small or did not adjust for known risk factors for cardiovascular disease.(6,15,16) Our study included 29,380 women who had hysterectomies, nearly equally divided between bilateral oophorectomy and ovarian conservation. Although baseline characteristics differed somewhat between groups, we used multivariable analysis to correct for multiple known risk-factors associated with all the conditions of interest. Follow-up over the 24 years was high for reported incident diagnoses and updated information on risk factors, and identification of deaths is about 98% complete.

Several limitations of our study deserve comment. The study was observational and oophorectomy or ovarian conservation was self-selected. Despite the biologic plausibility of many of our results and despite accounting for multiple risk factors, it is possible that our findings could be related to the underlying indication for which participants chose oophorectomy or due to uncorrected differences between the groups. Most of the women in this study were white and the results may not be applicable to non-white women.

Our results for cardiovascular disease are biologically plausible and supported by experimental evidence. Reduction in endogenous estrogen increases serum lipids, reduces carotid artery blood flow, and increases sub-clinical atherosclerosis as measured by carotid artery intima-media thickness.(17,18,19)

Our results are consistent with other studies. A decision analysis found that ovarian conservation improved survival for women younger than 65 at the time of surgery.(20) A cohort study of 1,097 women who underwent hysterectomy and bilateral oophorectomy for benign disease who were matched by age to 2,390 woman choosing ovarian conservation found mortality to be higher in women who had prophylactic bilateral oophorectomy before the age of 45 years.(16)

Earlier age of surgical or natural menopause correlates with increased risk of cardiovascular events.(15, 21, 22) Previous reports from the Nurses' Health Study found that women with

oophorectomy between ages 40-44, compared with women with intact ovaries, had double the risk of myocardial infarction (RR 2.2 95% CI 1.2, 4.2).(7) Oophorectomy after age 50 increased the risk of developing a first MI compared to controls (RR 1.4, 95% CI 1.0-2.0). (8) When adjusted for age, death from stroke was reduced 6% per year of delayed menopause (RR 0.94 95%CI 0.89, 1.00).(6) A meta-analysis of observational studies found that oophorectomy doubled the risk of cardiovascular disease (RR 2.62 95% CI 2.05, 3.35). (9) In that cardiovascular disease is the main cause of death among US women, any increased risk would be expected to increase overall morbidity and mortality, as found in our study.

Ovarian cancer is a low-prevalence disease, and simple hysterectomy may reduce the risk of ovarian cancer. Suggested mechanisms include interruption of transport of potential carcinogens through the reproductive tract, alteration in hormone levels or induction of protective anti-MUC1 antibodies. (23, 24, 25) Our analysis found a decreased risk of breast cancer among women following oophorectomy. Women with oophorectomy before age 50 have been shown to have a 50% decreased risk of breast cancer which persisted for 10 years following surgery.(26)

We found the increased risk of dying of other cancers exceeded the risk of dying from ovarian cancer (low incidence) and breast cancer (high long-term survival rate) among women having an oophorectomy. The association of oophorectomy with lung cancer was unexpected and warrants further study.

While postmenopausal estrogen therapy may reduce some of the increased risks we found, following publication of the WHI results many women discontinued hormone therapy and 77% fewer women now start hormones at the time of menopause.(27) Likewise, continuation rates for medications that can reduce the risk of cardiovascular disease, such as statins, are as low as 18% for women after one year. (28)

Our findings provide evidence that, for women not at high risk for ovarian cancer, oophorectomy may adversely affect long-term health outcomes and mortality and at no age was oophorectomy associated with a survival benefit. Preventive surgery should not be performed if it does not clearly benefit the patient. Therefore, prophylactic oophorectomy, with the goal of improving survival by reducing ovarian cancer, appears not to be supported by our study. Given that approximately 300,000 U.S. women a year undergo elective oophorectomy, these findings have important public health implications.

Acknowledgments

The authors thank the women in The Nurses' Health Study for their continuing contributions to the understanding of long-term health outcomes, and Dr. Shelley Tworoger, PhD and Dr. Bernard Rosner, PhD, for providing their advice on the study design and statistical analyses without compensation.

Funding: Funded by grants from Ethicon Women's Health and Partnership for Health Analytic Research.

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Table 1

Baseline* characteristics of the study population by oophorectomy status at hysterectomy

Variables	Ovarian Conservation (N=13,035; 44.4%)	Both Ovaries Removed (N=16,345; 55.6%)
Age: Mean (SD)	50.3 (8.0)	51.9 (6.8)
Age at Hysterectomy: Mean (SD)	43.3 (9.6)	46.8 (8.5)
Diabetes: %	3.3	3.7
High Blood Pressure: %	22.2	26.5
Hypercholesterolemia: %	12.2	17.2
Family History of MI before Age 60: %	17.4	16.8
Tubal Ligation: %	10.8	14.6
Family History of Breast Cancer: %	17.4	16.4
BMI in 1976 (%)		
<25	70.2	69.7
25-<30	21.3	21.0
>=30	7.6	8.3
Unknown/Missing	0.9	1.0
Smoking Status		
Past Smoker (%)	29.5	32.0
Years Since Quit Smoking, Mean (SD)	14.8 (10.2)	15.6 (10.3)
Current Smoker (%)	23.2	20.6
Cigarettes/day among Current Smokers, Mean (SD)	20.3 (10.8)	19.7 (10.4)
ET Use		
Past/Current Users (%)	36.0	78.3
Years of ET Use among Past/Current Users, Mean (SD)	4.5 (4.6)	4.1 (4.4)
OC Use		
Past OC Users (%)	49.5	47.4
Years of OC Use among Past Users, Mean (SD)	3.7 (3.6)	3.6 (3.7)
Parity		
Parous (%)	93.8	89.9
Number of Children among Parous Women, Mean (SD)	3.3 (1.4)	3.0 (1.3)
Alcohol Consumption		
Drinkers (%)	58.2	54.5
Alcohol Intake g/day, Mean (SD)	9.4 (11.6)	9.0 (11.3)
Physical Activity (hr/wk): Mean	3.0	2.9
ASA Use		
ASA Current Users (%)	35.9	35.4
Years of ASA Use Among Current Users, Mean (SD)	15.7 (12.5)	14.4 (12.6)

SD=standard deviation

*For each participant, baseline is her time of hysterectomy when she began follow-up for this analysis

Table 2

Risk of incident events (cancers) by oophorectomy status at time of hysterectomy

Event		Age at Hysterectomy			
		< 45 Years	45-54 Years	≥ 55 Years	All
Breast Cancer	**Ovarian Conservation** *				
	Cases, N	507	205	63	775
	Incidence rate per 100,000 PY	315	385	444	339
	Both Ovaries Removed				
	Cases, N	292	520	83	895
	Incidence rate per 100,000 PY	222	363	445	305
	Age-adjusted HR (95% CI)	**0.67 (0.58, 0.78)**	0.94 (0.80, 1.11)	1.04 (0.75, 1.44)	**0.84 (0.76, 0.93)**
	Multivariate† HR (95% CI)	**0.62 (0.53, 0.74)**	0.89 (0.75, 1.06)	1.05 (0.71, 1.55)	**0.75 (0.68, 0.84)**
Ovarian Cancer	**Ovarian Conservation** *				
	Cases, N	67	21	11	99
	Incidence rate per 100,000 PY	40	38	75	42
	Both Ovaries Removed				
	Cases, N	2	2	1	5
	Incidence rate per 100,000 PY	1	1	5	2
	Age-adjusted HR (95% CI)	**0.03 (0.01, 0.14)**	**0.04 (0.01, 0.16)**	**0.07 (0.01, 0.60)**	**0.04 (0.01, 0.09)**
Lung Cancer	**Ovarian Conservation** *				
	Cases, N	118	39	13	170
	Incidence rate per 100,000 PY	71	71	89	72
	Both Ovaries Removed				
	Cases, N	141	121	22	284
	Incidence rate per 100,000 PY	105	82	115	94
	Age-adjusted § HR (95% CI)	**1.34 (1.05, 1.72)**	1.21 (0.84, 1.74)	1.54 (0.79, 2.99)	1.17 (0.97, 1.42)
	Multivariate‡ HR (95% CI)	1.21 (0.91, 1.61)	1.30 (0.87, 1.94)	n/a**	**1.26 (1.02, 1.56)**
Colorectal Cancer	**Ovarian Conservation** *				
	Cases, N	92	41	21	154
	Incidence rate per 100,000 PY	56	74	145	66
	Both Ovaries Removed				
	Cases, N	96	113	25	234
	Incidence rate per 100,000 PY	72	77	131	78
	Age-adjusted HR (95% CI)	1.20 (0.90, 1.61)	1.04 (0.73, 1.49)	0.99 (0.56, 1.77)	1.08 (0.88, 1.32)
	Multivariate‡ HR (95% CI)	1.36 (0.98, 1.89)	1.16 (0.79, 1.72)	1.11 (0.49, 2.51)	1.23 (0.98, 1.54)

Event		Age at Hysterectomy			
		< 45 Years	**45-54 Years**	**≥ 55 Years**	**All**
Total Cancer	**Ovarian Conservation** *				
	Cases, N	1121	439	156	1716
	Incidence rate per 100,000 PY	712	841	1128	768
	Both Ovaries Removed				
	Cases, N	837	1147	199	2183
	Incidence rate per 100,000 PY	651	822	1089	762
	Age-adjusted HR (95% CI)	**0.86 (0.79, 0.95)**	0.99 (0.89, 1.10)	1.02 (0.82, 1.26)	**0.92 (0.86, 0.98)**
	Multivariate‡ HR (95% CI)	**0.83 (0.75, 0.92)**	0.95 (0.85, 1.07)	1.01 (0.79, 1.29)	**0.90 (0.84, 0.96)**

PY= person-year; CI=confidence interval; HR=hazard ratio;

*Reference group

**Sample size is too small. No multivariate analysis was conducted.

†Adjusted for age at hysterectomy, hypercholesterolemia, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, and total hours of weekly physical activity.

‡Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

§For lung cancer, risk estimates for all women were not encompassed by those within strata of age at hysterectomy due to confounding by age and age at hysterectomy and the high correlation between these variables.

Table 3

Risk of incident events (non-cancers) by oophorectomy status at time of hysterectomy

Event		Age at Hysterectomy			
		< 45 Years	**45-54 Years**	**≥ 55 Years**	**All**
Coronary Heart Disease	**Ovarian Conservation** *				
	Cases, N	240	105	35	380
	Incidence rate per 100,000 PY	147	193	243	163
	Both Ovaries Removed				
	Cases, N	281	294	42	617
	Incidence rate per 100,000 PY	212	201	222	207
	Age-adjusted HR (95% CI)	**1.34 (1.13, 1.60)**	1.08 (0.86, 1.35)	0.99 (0.64, 1.54)	**1.15 (1.01, 1.30)**
	Multivariate †† HR (95% CI)	**1.26 (1.04, 1.54)**	1.07 (0.84, 1.37)	1.31 (0.73, 2.36)	**1.17 (1.02, 1.35)**
Stroke	**Ovarian Conservation** *				
	Cases, N	198	87	36	321
	Incidence rate per 100,000 PY	120	159	250	137
	Both Ovaries Removed				
	Cases, N	211	276	46	533
	Incidence rate per 100,000 PY	159	189	243	179
	Age-adjusted § HR (95% CI)	**1.21 (1.00, 1.47)**	1.20 (0.94, 1.53)	1.17 (0.76, 1.80)	**1.17 (1.02, 1.34)**
	Multivariate †† HR (95% CI)	1.19 (0.96, 1.49)	1.20 (0.93, 1.55)	1.51 (0.86, 2.64)	1.14 (0.98, 1.33)
Hip Fracture	**Ovarian Conservation** *				
	Cases, N	98	41	24	163
	Incidence rate per 100,000 PY	59	75	166	70
	Both Ovaries Removed				
	Cases, N	67	116	18	201
	Incidence rate per 100,000 PY	50	79	94	67
	Age-adjusted HR (95% CI)	0.79 (0.58, 1.08)	1.07 (0.75, 1.53)	0.60 (0.33, 1.09)	0.87 (0.71, 1.07)
	Multivariate ‡ HR (95% CI)	0.81 (0.56, 1.17)	1.08 (0.73, 1.59)	0.65 (0.27, 1.57)	0.89 (0.71, 1.12)
Pulmonary Embolism	Ovarian Conservation *				
	Cases, N	55	19	13	87
	Incidence rate per 100,000 PY	33	34	89	37
	Both Ovaries Removed				
	Cases, N	63	62	7	132
	Incidence rate per 100,000 PY	47	42	37	44
	Age-adjusted HR (95% CI)	1.34 (0.94, 1.92)	1.30 (0.78, 2.16)	0.46 (0.18, 1.15)	1.11 (0.85, 1.45)

Event	Age at Hysterectomy			
	< 45 Years	45-54 Years	≥ 55 Years	All
Multivariate†† HR (95% CI)	1.31 (0.87, 1.98)	1.17 (0.67, 2.03)	n/a**	1.14 (0.85, 1.54)

PY=person-year; CI=confidence interval; HR=hazard ratio;

*Reference group

#Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

††Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

§For stroke, risk estimates for all women were not encompassed by those within strata of age at hysterectomy due to confounding by age and age at hysterectomy and the high correlation between these variables.

Table 4

Risk of cause-specific and all-cause death by oophorectomy status at time of hysterectomy

Event		Age at Hysterectomy			
		< 45 Years	**45-54 Years**	**≥ 55 Years**	**All**
Breast Cancer	**Ovarian Conservation** *				
	Cases, N	64	27	6	97
	Incidence rate per 100,000 PY	39	49	41	41
	Both Ovaries Removed				
	Cases, N	43	80	10	133
	Incidence rate per 100,000 PY	32	54	52	44
	Age-adjusted HR (95% CI)	0.78 (0.53, 1.15)	1.11 (0.71, 1.72)	1.28 (0.46, 3.54)	0.96 (0.74, 1.25)
	Multivariate † HR (95% CI)	0.74 (0.47, 1.18)	1.14 (0.70, 1.85)	n/a **	0.94 (0.70, 1.26)
Ovarian Cancer **	**Ovarian Conservation** *				
	Cases, N	21	10	3	34
	Incidence rate per 100,000 PY	13	18	21	14
	Both Ovaries Removed				
	Cases, N	1	2	0	3
	Incidence rate per 100,000 PY	1	1	0	1
	Age-adjusted HR (95% CI)	**0.06 (0.01, 0.43)**	**0.07 (0.02, 0.35)**	n/a	**0.06 (0.02, 0.21)**
Lung Cancer	**Ovarian Conservation** *				
	Cases, N	93	25	9	127
	Incidence rate per 100,000 PY	56	45	62	54
	Both Ovaries Removed				
	Cases, N	107	87	15	209
	Incidence rate per 100,000 PY	80	59	78	69
	Age-adjusted § HR (95% CI)	1.30 (0.98, 1.72)	1.35 (0.86, 2.11)	1.56 (0.69, 3.50)	1.14 (0.92, 1.43)
	Multivariate †† HR (95% CI)	1.13 (0.82, 1.56)	1.41 (0.85, 2.34)	n/a **	**1.31 (1.02, 1.68)**
Colorectal Cancer	**Ovarian Conservation** *				
	Cases, N	26	11	5	42
	Incidence rate per 100,000 PY	16	20	34	18
	Both Ovaries Removed				
	Cases, N	31	43	2	76
	Incidence rate per 100,000 PY	23	29	10	25
	Age-adjusted HR (95% CI)	1.43 (0.85, 2.38)	1.49 (0.77, 2.88)	0.33 (0.07, 1.61)	1.28 (0.88, 1.87)
	Multivariate †† HR (95% CI)	0.94 (0.47, 1.87)	1.81 (0.76, 4.28)	n/a **	1.15 (0.72, 1.86)

Event		Age at Hysterectomy			
		< 45 Years	**45-54 Years**	**≥ 55 Years**	**All**
Total Cancer	**Ovarian Conservation** *				
	Cases, N	355	134	40	529
	Incidence rate per 100,000 PY	214	242	274	225
	Both Ovaries Removed				
	Cases, N	352	410	61	823
	Incidence rate per 100,000 PY	262	277	318	273
	Age-adjusted HR (95% CI)	1.14 (0.99, 1.33)	1.17 (0.96, 1.42)	1.28 (0.86, 1.90)	1.10 (0.98, 1.22)
	Multivariate†† HR (95% CI)	1.08 (0.91, 1.27)	1.21 (0.98, 1.49)	1.49 (0.91, 2.45)	**1.17 (1.04, 1.32)**
Coronary Heart Disease	**Ovarian Conservation** *				
	Cases, N	81	31	13	125
	Incidence rate per 100,000 PY	49	56	89	53
	Both Ovaries Removed				
	Cases, N	103	107	15	225
	Incidence rate per 100,000 PY	77	72	78	75
	Age-adjusted HR (95% CI)	**1.41 (1.05, 1.89)**	1.33 (0.89, 2.00)	1.09 (0.54, 2.21)	**1.25 (1.00, 1.56)**
	Multivariate§ HR (95% CI)	1.14 (0.81, 1.61)	1.15 (0.73, 1.81)	4.10 (0.41, 41.06)	**1.28 (1.00, 1.64)**
Stroke	**Ovarian Conservation** *				
	Cases, N	49	24	6	79
	Incidence rate per 100,000 PY	30	43	41	34
	Both Ovaries Removed				
	Cases, N	52	74	14	140
	Incidence rate per 100,000 PY	39	50	73	46
	Age-adjusted HR (95% CI)	1.17 (0.80, 1.73)	1.17 (0.74, 1.85)	2.26 (0.85, 5.95)	1.23 (0.93, 1.62)
	Multivariate§ HR (95% CI)	0.85 (0.54, 1.34)	1.16 (0.70, 1.91)	n/a **	1.11 (0.82, 1.51)
All-cause death	**Ovarian Conservation** *				
	Cases, N	797	323	122	1242
	Incidence rate per 100,000 PY	481	584	836	527
	Both Ovaries Removed				
	Cases, N	830	977	148	1955
	Incidence rate per 100,000 PY	618	660	773	648
	Age-adjusted HR (95% CI)	**1.18 (1.07, 1.30)**	**1.17 (1.03, 1.32)**	1.10 (0.87, 1.40)	**1.10 (1.03, 1.18)**
	Multivariate‡ HR (95% CI)	1.06 (0.95, 1.18)	**1.15 (1.01, 1.32)**	1.14 (0.85, 1.52)	**1.12 (1.03, 1.21)**

PY=person-year; CI=confidence interval; HR=hazard ratio;

*Reference group

**Sample size is too small. No multivariate analysis was conducted.

†Adjusted for age at hysterectomy, hypercholesterolemia, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, and total hours of weekly physical activity.

††Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

§Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

‡Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, use of estrogen therapy, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

Table 5

Risk of incident events and all-cause death by oophorectomy status at time of hysterectomy among never-users of estrogen therapy

Event		Age at Hysterectomy		
		< 50 Years	**≥ 50 Years**	**All**
Breast Cancer	**Ovarian Conservation** *			
	Cases, N	176	20	196
	Incidence rate per 100,000 PY	267	276	268
	Both Ovaries Removed			
	Cases, N	33	34	67
	Incidence rate per 100,000 PY	234	469	314
	Age-adjusted HR (95% CI)	0.73 (0.50, 1.05)	**1.81 (1.03, 3.19)**	0.95 (0.72, 1.26)
	Multivariate‡ HR (95% CI)	0.66 (0.43, 1.03)	1.88 (0.66, 5.32)	0.85 (0.61, 1.20)
Ovarian Cancer	**Ovarian Conservation** *			
	Cases, N	12	2	14
	Incidence rate per 100,000 PY	18	27	19
	Both Ovaries Removed			
	Cases, N	0	0	0
	Incidence rate per 100,000 PY	0	0	0
Lung Cancer	**Ovarian Conservation** *			
	Cases, N	27	7	34
	Incidence rate per 100,000 PY	40	95	45
	Both Ovaries Removed			
	Cases, N	16	7	23
	Incidence rate per 100,000 PY	111	94	106
	Age-adjusted HR (95% CI)	1.89 (0.97, 3.66)	0.85 (0.29, 2.52)	1.45 (0.84, 2.50)
	Multivariate†† HR (95% CI)	2.36 (0.78, 7.17)	n/a **	**2.24 (1.07, 4.69)**
Coronary Heart Disease	**Ovarian Conservation** *			
	Cases, N	72	19	91
	Incidence rate per 100,000 PY	107	261	122
	Both Ovaries Removed			
	Cases, N	40	14	54
	Incidence rate per 100,000 PY	283	190	251
	Age-adjusted HR (95% CI)	**1.73 (1.17, 2.57)**	0.70 (0.34, 1.44)	1.33 (0.94, 1.87)
	Multivariate§ HR (95% CI)	**1.93 (1.14, 3.29)**	n/a **	1.41 (0.92, 2.15)
Stroke	**Ovarian Conservation** *			

Event		Age at Hysterectomy		
		< 50 Years	**≥ 50 Years**	**All**
	Cases, N	47	7	54
	Incidence rate per 100,000 PY	70	95	72
	Both Ovaries Removed			
	Cases, N	30	11	41
	Incidence rate per 100,000 PY	210	149	189
	Age-adjusted HR (95% CI)	**1.88 (1.18, 3.02)**	1.21 (0.48, 3.00)	**1.62 (1.08, 2.43)**
	Multivariate[§] HR (95% CI)	**2.10 (1.11, 3.99)**	n/a[**]	**1.82 (1.07, 3.11)**
All-Cause Death	**Ovarian Conservation** [*]			
	Cases, N	162	36	198
	Incidence rate per 100,000 PY	240	488	264
	Both Ovaries Removed			
	Cases, N	82	35	117
	Incidence rate per 100,000 PY	569	469	535
	Age-adjusted HR (95% CI)	**1.54 (1.17, 2.02)**	1.13 (0.71, 1.79)	**1.28 (1.01, 1.62)**
	Multivariate[†] HR (95% CI)	**1.40 (1.01, 1.96)**	2.05 (0.87, 4.79)	1.20 (0.91, 1.57)

PY=person-year; CI=confidence interval; HR=hazard ratio;

[*] Reference group

[**] Sample size is too small. No multivariate analysis was conducted.

[†] Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

[‡] Adjusted for age at hysterectomy, hypercholesterolemia, tubal ligation, family history of breast cancer, BMI in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, and total hours of weekly physical activity.

[††] Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, BMI in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.

[§] Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of MI before age 60, BMI in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and ASA use.