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

William H. Parker, MD, Michael S. Broder, MD, MPH, Eunice Chang, PhD, Diane Feskanich, ScD, Cindy Farquhar, MD, Zhimae Liu, PhD, Donna Shoupe, MD, Jonathan S. Berek, MD, MMS, Susan Hankinson, ScD, and JoAnn E. Manson, MD, DrPH

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 (HRs) were 1.12 (95% confidence interval [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, number needed to treat=220), and total cancers (HR 0.90, 95% CI 0.84–0.96) decreased after oophorectomy, lung cancer incidence (HR=1.26, 95% CI 1.02–1.56, number needed to harm=190), and total cancer mortality (HR=1.17, 95% CI 1.04–1.32) increased. For those never having used estrogen therapy, bilateral oophorectomy before age 50 years was associated with an increased risk of all-cause mortality, CHD, and stroke. With an approximate 35-year life span after surgery, one additional death would be expected for every nine oophorectomies performed.

CONCLUSION: 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 nonfatal coronary heart disease, and lung cancer. In no analysis or age group was oophorectomy associated with increased survival.

(Obstet Gynecol 2009;113:1027–37)

LEVEL OF EVIDENCE: II

From the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California; UCLA School of Medicine, Los Angeles, California; Partnership for Health Analytic Research, Los Angeles, California; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; School of Medicine, University of Auckland, Auckland, New Zealand; Cerner Health Insights, Beverly Hills, California; Keck School of Medicine, University of Southern California, Los Angeles, California; Stanford University School of Medicine, Stanford, California; Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

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

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 and Dr. Bernard Rosner for providing their advice on the study design and statistical analyses without compensation.

Corresponding author: Dr. William H. Parker, Department of Obstetrics and Gynecology, John Wayne Cancer Institute at Saint John's Health Center, 1450 10th Street, Santa Monica, CA 90401; e-mail: wparker@ucla.edu.

Financial Disclosure

Dr. Parker has been a consultant to Ethicon Women's Health (Cincinnati, 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.

ISSN: 0029-7844/09

Bilateral oophorectomy at the time of hysterectomy for benign disease is commonly practiced to prevent subsequent development of ovarian cancer.[1] Data from the Centers for Disease Control and Prevention show that for women having a hysterectomy between ages 40 years and 44 years, 50% have concurrent oophorectomy, and between ages 45 years

and 64 years, 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.[6–9] Among U.S. women, ovarian cancer accounts for 14,700 deaths per year, whereas coronary heart disease accounts for 326,900 deaths, and stroke accounts 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

We used the database from the Nurses' Health Study cohort, which included 122,700 married registered nurses who were aged 30–55 years in 1976 when the initial questionnaires were mailed. Race was self-reported and the cohort was 94% white, 2% African American, 1% Asian, 1% multiracial, 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 2 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] Nurses' Health Study 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 Nurses' Health Study participants were initially included before application of exclusion criteria.

Through 2002, 50,432 Nurses' Health Study 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) before 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.

We focused on incident events and death due to the following conditions: coronary heart disease (International Classification of Diseases, 8th Revision [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]

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 myocardial infarction 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 use, alcohol consumption, physical activity and acetylsalicylic acid use (Table 1). Alcohol consumption, physical activity, and use of acetylsalicylic acid 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.

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

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 (y)	50.3±8.0	51.9±6.8
Age at hysterectomy (y)	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 y	17.4	16.8
Tubal ligation	10.8	14.6
Family history of breast cancer	17.4	16.4
BMI in 1976		
Less than 25	70.2	69.7
25 to less than 30	21.3	21.0
More than 30	7.6	8.3
Unknown/missing	0.9	1.0
Smoking status		
Past smoker	29.5	32.0
Years since quit smoking	14.8±10.2	15.6±10.3
Current smoker	23.2	20.6
Cigarettes/day among current smokers	20.3±10.8	19.7±10.4
ET use		
Past/current users	36.0	78.3
Years of use among past/current users	4.5±4.6	4.1±4.4
OC use		
Past users	49.5	47.4
Years of use among past users	3.7±3.6	3.6±3.7
Parity		
Parous	93.8	89.9
Number of children among parous women	3.3±1.4	3.0±1.3
Alcohol consumption		
Drinkers	58.2	54.5
Alcohol intake (g/day)	9.4±11.6	9.0±11.3
Mean physical activity (h/wk)	3.0	2.9
ASA use		
ASA current users	35.9	35.4
Years of ASA use among current users	15.7±12.5	14.4±12.6

MI, myocardial infarction; BMI, body mass index; ET, estrogen therapy; OC, oral contraceptive pill; ASA, acetylsalicylic acid.
Data are mean±standard deviation or % unless otherwise indicated.
* For each participant, baseline is her time of hysterectomy when she began follow-up for this analysis.

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 (CIs). 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 subcohorts based on age at hysterectomy: younger than 45 years, 45–54 years, and 55 years or older, and we conducted modeling separately for each. In a secondary analysis of oophorectomy status among those who never used estrogen therapy, women were stratified into two age groups (younger than 50 years and 50 years or older) to gain statistical power, and all analyses were repeated. All data transformations and statistical analyses were performed using SAS 9.1. (SAS Institute Inc., Cary, NC) All *P* values were based on two-tailed 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 2. Risk of Incident Events (Cancers) by Oophorectomy Status at Time of Hysterectomy

	Age at Hysterectomy			
Event	Younger Than 45 y	45–54 y	55 y or Older	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)	NA‖	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)
Total cancer				
Ovarian conservation*				
Cases (n)	1,121	439	156	1,716
Incidence rate per 100,000 PY	712	841	1,128	768
Both ovaries removed				
Cases (n)	837	1,147	199	2,183
Incidence rate per 100,000 PY	651	822	1,089	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; HR, hazard ratio; CI, confidence interval; NA, not analyzed.

* Reference group.

† Adjusted for age, age at hysterectomy, hypercholesterolemia, tubal ligation, family history of breast cancer, body mass index 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.

‡ 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.

§ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, body mass index 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 acetylsalicylic acid use.

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

¶ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, tubal ligation, body mass index 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 acetylsalicylic acid use.

(Table 1). After adjustment for multiple relevant risk factors, we compared the two groups in relation to the incidence of fatal and nonfatal events during 24 years of follow-up (Table 2—cancer events, Table 3— noncancer 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 years (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 years (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

Table 3. Risk of Incident Events (Noncancers) by Oophorectomy Status at Time of Hysterectomy

	Age at Hysterectomy			
Event	Younger Than 45 y	45–54 y	55 y or Older	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)
Multivariate† HR (95% CI)	1.31 (0.87–1.98)	1.17 (0.67–2.03)	NA‖	1.14 (0.85–1.54)

PY, person-year; HR, hazard ratio; CI, confidence interval; NA, not analyzed.

* Reference group.

† Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, body mass index 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 acetylsalicylic acid 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.

§ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, tubal ligation, family history of breast cancer, body mass index 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 acetylsalicylic acid use.

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

Table 4. Risk of Cause-Specific and All-Cause Death by Oophorectomy Status at Time of Hysterectomy

	Age at Hysterectomy			
Event	Younger Than 45 y	45–54 y	55 y or Older	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)	1.16 (0.71–1.88)	NA‡	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)	NA	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 (0.85–2.33)	NA‡	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)	1.08 (0.59–1.96)	2.01 (0.96–4.31)	NA‡	1.35 (0.88–2.06)
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)	1.50 (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)

(*continued*)

Table 4. Risk of Cause-Specific and All-Cause Death by Oophorectomy Status at Time of Hysterectomy (*continued*)

	Age at Hysterectomy			
Event	Younger Than 45 y	45–54 y	55 y or Older	All
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)	NA‡	1.11 (0.82–1.51)
All-cause death				
Ovarian Conservation*				
Cases (n)	797	323	122	1,242
Incidence rate per 100,000 PY	481	584	836	527
Both ovaries removed				
Cases (n)	830	977	148	1,955
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; HR, hazard ratio; CI, confidence interval; NA, not analyzed.

* Reference group.

† Adjusted for age at hysterectomy, hypercholesterolemia, tubal ligation, family history of breast cancer, body mass index 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.

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

§ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, body mass index 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 acetylsalicylic acid use.

‖ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, body mass index 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 acetylsalicylic acid use.

¶ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, tubal ligation, body mass index 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 acetylsalicylic acid use.

Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, tubal ligation, family history of breast cancer, body mass index 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 acetylsalicylic acid use.

of lung cancer (HR 1.26, 95% CI 1.02–1.56), and a reduction in total cancers (HR 0.90, 95% CI 0.84–0.96). 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%) died from stroke, 230 (7.2%) died from breast cancer, 37 (1.2%) died from ovarian cancer, 336 (10.5%) died from lung cancer, 118 (3.7%) died from colorectal cancer, none died due to hip fracture, 12 (0.4%) died from pulmonary embolism, and 1,895 (59.3%) died from other causes.

Among women having a simple hysterectomy, 1,242 died (527 per 100,000 person-years), and among women having a hysterectomy with bilateral oophorectomy, 1,955 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.

Table 5. Risk of Incident Events and All-Cause Death by Oophorectomy Status at Time of Hysterectomy Among Those Who Never Used Estrogen Therapy

Event	Age at Hysterectomy		
	Younger Than 50 y	50 y or Older	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)	NA§	2.09 (1.01–4.33)
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)	1.98 (1.18–3.32)	NA§	1.42 (0.93–2.16)
Stroke			
Ovarian conservation*			
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)	2.19 (1.16–4.14)	NA§	1.85 (1.09–3.16)
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; HR, hazard ratio; CI, confidence interval; NA, not analyzed.

* Reference group.

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

‡ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, body mass index in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and acetylsalicylic acid use.

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

‖ Adjusted for age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, body mass index in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and acetylsalicylic acid use.

¶ Adjusted for age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, tubal ligation, family history of breast cancer, body mass index in 1976, smoking status, duration of oral contraceptive use, parity, average daily alcohol consumption, total hours of weekly physical activity, and acetylsalicylic acid use.

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 younger than 50 years and 50 years or older (Table 5). Those who never used ET who had oophorectomy before age 50 years 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 aged younger than 50 years 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 aged younger than 50 years 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 years 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 Nurses' Health Study cohort is particularly homogenous relative to a study in the general population, with regard to educational and socioeconomic factors that may possibly confound nonrandomized studies. 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. 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 report (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 approximately 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 nonwhite 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 subclinical atherosclerosis as measured by carotid artery intima-media thickness.[17–19]

Our results are consistent with other studies. A decision analysis found that ovarian conservation improved survival for women aged younger than 65 years 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 women 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 the ages of 40 years and 44 years, 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 years increased the risk of developing a first myocardial infarction compared with 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 U.S. 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.[23–25] Our analysis found a decreased risk of breast cancer among women after oophorectomy. Women with oophorectomy before age 50 years have been shown to have a 50% decreased risk of breast cancer that persisted for 10 years after 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.

Although postmenopausal estrogen therapy may reduce some of the increased risks we found, after publication of the Women's Health Initiative 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, seems not to be supported by our study. Given that approximately 300,000 U.S. women per year undergo elective oophorectomy, these findings have important public health implications.

REFERENCES

1. ACOG. ACOG Practice Bulletin No. 89. Elective and risk-reducing salpingo-oophorectomy. Obstet Gynecol 2008;111:231–41.
2. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP), 1988–2001: a federal-state-industry partnership in health data. July 2003. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm. Retrieved March 10, 2009.
3. Judd H, Judd G, Lucas W, Yen S. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 1974;39:1020–4.
4. Fogle R, Stanczyk F, Zhang X, Paulson R. Ovarian androgen production in postmenopausal women. J Clin Endocrinol Metab 2007;92:3040–3.
5. Judd H, Lucas W, Yen S. Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet Gynecol 1974;118:793–8.
6. Ossewaarde M, Bots M, Verbeek A, Peeters PH, van der Graaf Y, Grobbee DE, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology 2005;16:556–62.
7. Colditz G, Willett W, Stampfer M, Rosner B, Speizer F, Hennekens C. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316:1105–10.
8. Falkeborn M, Schairer C, Naessen T, Persson I. Risk of myocardial infarction after oophorectomy and hysterectomy. J Clin Epidemiol 2000;53:832–7.
9. Atsma F, Bartelink M, Grobbee D, van der Schouw Y. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause 2006;13:265–79.
10. Kung H, Hoyert D, Xu J, Murphy S. Deaths: Final Data for 2005. Natl Vital Stat Rep 2008;56:1–120.
11. Armstrong K, Schwartz J, Randall T, Rubin S, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol 2004;22:1045–54.
12. Colditz G, Manson J, Hankinson S. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62.
13. Colditz G, Stampfer M, Willett W, Stason W, Rosner B, Hennekens C, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. Am J Epidemiol 1987;126:319–25.
14. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
15. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714–8.
16. Rocca W, Grossardt B, de Andrade M, Malkasian G, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 2006;7:821–8.
17. Cheung L, Pang M, Lam C, Tomlinson B, Chung T, Haines C. Acute effects of a surgical menopause on serum concentrations of lipoprotein(a). Climacteric 1998;1:33–41.

18. Mihmanli V, Mihmanli I, Kantarci F, Aydin T, Yilmaz M, Ogut G. Carotid pulsatility indices in surgical menopause. Arch Gynecol Obstet 2002;266:96–100.
19. Hodis H, Mack W. Atherosclerosis imaging methods: assessing cardiovascular disease and evaluating the role of estrogen in the prevention of atherosclerosis. Am J Cardiol 2002;89:19E–27E.
20. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol 2005;106:219–26.
21. Løkkegaarda E, Jovanovicb Z, Heitmannc B, Keidingb N, Ottesend B, Pedersend A. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. Maturitas 2006;53:226–33.
22. de Kleijn M, van der Schouw Y, Verbeek A, Peeters P, Banga J, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. Am J Epidemiol 2002;155:339–45.
23. Hankinson S, Hunter D, Colditz G, Willett W, Stampfer M, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. JAMA 1993;270:2813–8.
24. Cramer DW, Welch WR, Berkowitz RS, Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. Obstet Gynecol 2007;110:498–501.
25. Cramer D, Titus-Ernstoff L, McKolanis J, Welch W, Vitonis A, Berkowitz R, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1125–31,
26. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton L. Breast cancer risk associated with gynecologic surgery and indications for such surgery. Int J Cancer 1997; 70:150–4.
27. Wegienka G, Havstad S, Kelsey J. Menopausal hormone therapy in a health maintenance organization before and after women's health initiative hormone trials termination. J Womens Health (Larchmt) 2006;15:369–78.
28. Huser MA, Evans TS, Berger V. Medication adherence trends with statins. Adv Ther 2005;22:163–71.