Long-Term Mortality Associated With Oophorectomy Compared With Ovarian Conservation in the Nurses' Health Study

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OBJECTIVE: To report long-term mortality after oophorectomy or ovarian conservation at the time of hysterectomy in subgroups of women based on age at the time of surgery, use of estrogen therapy, presence of risk factors for coronary heart disease, and length of follow-up.

METHODS: This was a prospective cohort study of 30,117 Nurses' Health Study participants undergoing hysterectomy for benign disease. Multivariable adjusted hazard ratios for death from coronary heart disease, stroke, breast cancer, epithelial ovarian cancer, lung cancer, colorectal cancer, total cancer, and all causes were determined comparing bilateral oophorectomy (n=16,914) with ovarian conservation (n=13,203).

RESULTS: Over 28 years of follow-up, 16.8% of women with hysterectomy and bilateral oophorectomy died from all causes compared with 13.3% of women who had ovarian conservation (hazard ratio 1.13, 95% confidence interval 1.06–1.21). Oophorectomy was associated with a lower risk of death from ovarian cancer (four women with oophorectomy compared with 44 women with ovarian conservation) and, before age 47.5 years, a lower risk of death from breast cancer. However, at no age was oophorectomy associated with a lower risk of other cause-specific or all-cause mortality. For women younger than 50 years at the time of hysterectomy, bilateral oophorectomy was associated with significantly increased mortality in women who had never used estrogen therapy but not in past and current users: assuming a 35-year lifespan after oophorectomy: number needed to harm for all-cause death=8, coronary heart disease death=33, and lung cancer death=50.

CONCLUSIONS: Bilateral oophorectomy is associated with increased mortality in women aged younger than 50 years who never used estrogen therapy and at no age is oophorectomy associated with increased survival.

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Each year approximately 610,000 U.S. women undergo hysterectomy for benign disease and 23% of women aged 40–44 years and 45% of women aged 45–49 years have concomitant elective oophorectomy to prevent the subsequent development of ovarian cancer.[1,2]

Bilateral oophorectomy, when compared with ovarian conservation, is associated with a decreased risk of ovarian cancer but may increase risks of death from coronary heart disease (CHD) and all causes.[3,4] Although some studies are not consistent with these findings, they include small numbers of women, have short-term or delayed onset of follow-up, or compared oophorectomy with natural menopause.[5,6]

The Nurses' Health Study is an ongoing prospective observational study of women and health outcomes. In a previous investigation over 24 years of follow-up,

we found that bilateral oophorectomy, compared with ovarian conservation, at the time of hysterectomy was associated with a lower risk of incident ovarian and breast cancer but a higher risk of incident CHD, stroke, lung cancer and total cancers, and mortality from all causes.[7]

In this further analysis of updated data from the Nurses' Health Study, we focused on all-cause and cause-specific mortality and addressed clinical issues raised by earlier publications. Specifically, we examined bilateral oophorectomy compared with ovarian conservation in women aged 60 years or older and determined whether there was an age at which oophorectomy confers a survival benefit. We also conducted analyses in several subgroups of women who we hypothesized would experience a more elevated mortality after bilateral oophorectomy, including women who underwent hysterectomy before age 50 years who never used estrogen therapy; women with known risk factors for cardiovascular disease; women with a family history of breast or ovarian cancer; and women who smoked. Finally, we examined cardiovascular disease mortality associated with oophorectomy status in women who were observed for 15 years or longer after hysterectomy to ascertain whether long-term follow-up is important for this research.

MATERIALS AND METHODS

The Nurses' Health Study cohort includes 121,700 female registered nurses in the United States who were aged 30–55 years when they completed the initial mailed questionnaires in 1976. Participants provided detailed information about medical history and risk factors for cancer, heart disease, and other diseases. Information has been updated on biennial follow-up questionnaires with response rates of approximately 90% for each cycle.[8] The cohort was relatively homogenous with regard to education, socioeconomic status, and access to health care. Race was self-reported: 94% white, 2% African American, 1% Asian, 1% multiracial, and 2% other.

Nurses' Health Study participants with a prior hysterectomy entered study follow-up in 1980, when information was available for all relevant risk factors. Other participants entered when they reported undergoing hysterectomy on the 1982 through 2006 questionnaires. Overall, 52,157 Nurses' Health Study participants reported undergoing hysterectomy without a diagnosis of gynecologic cancer. We excluded 9,380 women with a history of other cancers, CHD, stroke, or pulmonary embolus; 4,909 with unilateral or partial oophorectomy; 4,869 with unknown age at hysterectomy; 2,559 with unknown ovarian status at the time of hysterectomy; and 555 with oophorectomy before or after, rather than at the time of, hysterectomy. The remaining 30,117 women were included in the analysis; 16,914 (56.2%) underwent hysterectomy with bilateral oophorectomy, and 13,203 (43.8%) underwent hysterectomy with ovarian conservation. Submission of completed self-administered questionnaires was deemed to imply informed consent. The institutional review boards at John Wayne Cancer Institute at Saint John's Health Center in Santa Monica, California, and Brigham and Women's Hospital in Boston, Massachusetts, approved this study.

Nurses' Health Study participants completed mailed, biennial follow-up questionnaires on which they reported age, age at hysterectomy, parental history of myocardial infarction before age 60 years, tubal ligation, parity, family history of breast cancer, family history of ovarian cancer, diabetes, high blood pressure, hypercholesterolemia, smoking status, duration of oral contraceptive use, use of estrogen therapy, alcohol consumption, physical activity, and aspirin use. Body mass index (BMI, calculated as weight (kg)/[height (m)]^2) from the initial 1976 questionnaire was used for the analysis. A validation study ascertained that self-report of oophorectomy was more than 90% accurate as compared with medical records.[9] For estrogen therapy use before 1976, age at initiation, doses, types, and routes of administration could not be examined because they were not ascertained on early questionnaires. For all variables, missing information was separately noted.

We identified deaths using the National Death Index and by reports of next of kin, which was more than 98% complete.[10] Date and cause of death were determined using death certificates, autopsy reports, and medical records. We assessed deaths resulting from the following conditions: CHD, stroke, breast cancer, epithelial ovarian cancer, lung cancer, colorectal cancer, total cancer, and all causes.

Women contributed person-time from the return of the 1980 questionnaire or a later questionnaire after incident hysterectomy and were censored at oophorectomy subsequent to hysterectomy, death, or the end of follow-up on June 1, 2008. We used Cox proportional hazards models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) comparing bilateral oophorectomy with ovarian conservation. Analyses were stratified by age and questionnaire cycle and were controlled for relevant risk factors. We conducted modeling separately for three subcohorts based on age at hysterectomy: younger than 50 years, 50–59 years, and 60 years or older. For this and other stratified analyses, we used the

significance of the interaction term between the exposure and the stratifying variable to test whether results were statistically different across strata ($P_{interaction}$).

We were interested in potential confounding by diabetes, high blood pressure, and hypercholesterolemia before hysterectomy. However, 47% of women underwent hysterectomy before they entered the cohort in 1976 and we did not include these risk factors in the primary models. In a sensitivity analysis, we included these factors reported in 1976 for women who underwent hysterectomy before 1976; for those who underwent hysterectomy after 1976, we used the status of these risk factors just before surgery. Results of the sensitivity analysis were very similar to those reported in the primary models (data not shown).

We constructed models with age at hysterectomy as a continuous independent variable to examine whether there was an age at which oophorectomy conferred survival benefit. For each outcome, linear and quadratic models were conducted and compared. In the linear model, age at hysterectomy was included with other covariates. In the quadratic model, a linear term and a quadratic term of age at hysterectomy were included. We performed a likelihood ratio test to determine whether the quadratic model would be a better fit and, if so, the cutoff point at which age at hysterectomy conferred survival benefit was estimated. The cutoff point is the age that achieves the highest (for concave down shape) or lowest (for concave up shape) value of the quadratic equation.

We conducted several stratified analyses to assess the association between oophorectomy and mortality in targeted subgroups. In women who underwent hysterectomy before age 50 years, we assessed all-cause and cause-specific mortality in relation to oophorectomy in women who never used estrogen therapy and compared these results with those in past and current estrogen therapy users. We also examined the risk of all-cause and cardiovascular disease mortality associated with bilateral oophorectomy stratified by the presence of risk factors for cardiovascular disease: diabetes, hypertension, hypercholesterolemia, current smoker, BMI greater than 30 in 1976, or parental history of myocardial infarction before age 60 years. Women were considered high risk if they had two or more risk factors and low risk if they had zero or one risk factor. This analysis was limited to women who underwent hysterectomy after entering the cohort in 1976 (n=16,395) for whom the presence of cardiovascular disease risk factors could be ascertained at the time of hysterectomy. Other stratified analyses were conducted by smoking status and by family history of breast or ovarian cancer.

Autopsy studies suggest that after oophorectomy, cardiovascular disease takes approximately 15 years to develop.[11] Therefore, prolonged follow-up would be necessary to detect an association with increased cardiovascular disease mortality. We conducted a subset analysis of women who had 15 or more years of follow-up subsequent to their hysterectomy. We excluded women who died (n=835) or had cardiovascular disease outcome (n=519) within 15 years of surgery and women who had less than 15 years of follow-up after hysterectomy (n=5,421). Within this subgroup, we compared women with bilateral oophorectomy (n=13,118) with those who had ovarian conservation (n=10,093). All data transformations and statistical analyses were performed using SAS 9.2. All *P* values were based on two-tailed tests with significance of .05.

RESULTS

Baseline characteristics stratified by age at hysterectomy (younger than 50, 50–59, 60 years or older) and oophorectomy status are presented in Table 1. Most characteristics were similar across strata. Data were missing for less than 5% of participants for all variables except duration of estrogen therapy use, alcohol consumption, and aspirin use.

In the analysis of all women with hysterectomy (Fig. 1), 2,850 (16.8%) women with bilateral oophorectomy died from all causes compared with 1,749 (13.3%) women who had ovarian conservation. Forty-four women with ovarian conservation and four with oophorectomy died from ovarian cancer over 28 years of follow-up (HR 0.06, 95% CI 0.02–0.17). Oophorectomy was associated with higher mortality from CHD (multivariable HR 1.23, 95% CI 1.00–1.52), lung cancer (HR 1.29, 95% CI 1.04–1.61), colorectal cancer (HR 1.49, 95% CI 1.02–2.18), total cancers (HR 1.16, 95% CI 1.05–1.29), and all causes (HR 1.13, 95% CI 1.06–1.21). Results were not statistically different for any of the mortality outcomes when stratified by age at hysterectomy. Although there were insufficient numbers to analyze some cause-specific deaths in women aged 60 years and older, risk estimates associated with bilateral oophorectomy remained elevated for all-cause, total cancer, and cardiovascular disease mortality in these older women. Among women with hysterectomy before age 50 years, oophorectomy was associated with significant increases in risk of deaths from CHD, colorectal cancer, total cancers, and all causes.

Multivariable analyses comparing models using either linear or linear plus quadratic terms for age at hysterectomy found that oophorectomy before age 47.5 years was associated with a lower risk of death from breast cancer (*P*=.048). However, similar comparisons

Table 1. Baseline Characteristics* of the Study Population by Age at Hysterectomy and Oophorectomy Status

	Age at Hysterectomy (y)					
	Younger Than 50		50–59		60 or Older	
	Ovarian Conservation (n=10,147)	Bilateral Oophorectomy (n=10,947)	Ovarian Conservation (n=1,746)	Bilateral Oophorectomy (n=4,495)	Ovarian Conservation (n=1,310)	Bilateral Oophorectomy (n=1,472)
Age (y)	47.8	49.1	56.1	55.2	68.5	67.6
Age at hysterectomy (y)	39.6	42.4	54.1	53.0	67.5	66.5
Diabetes	2.1	2.6	3.6	2.8	5.0	5.7
High blood pressure†	12.9	16.9	22.5	24.7	44.3	42.8
Hypercholesterolemia†	4.1	6.4	15.3	18.4	51.9	55.0
Tubal ligation	9.4	11.9	17.7	21.9	13.6	16.8
Family history						
MI before age 60 y	17.9	17.2	15.6	16.1	13.9	15.0
Breast cancer	18.8	17.6	21.0	18.7	20.1	19.0
Ovarian cancer	4.9	5.1	5.8	5.9	4.5	6.4
BMI in 1976 (kg/m^2)						
Less than 25	70.4	69.0	70.5	70.3	69.1	75.2
25–29.9	21.1	21.2	22.1	20.8	21.8	18.1
30 or greater	7.6	8.8	6.7	7.7	7.9	5.9
Smoking status						
Past smoker	27.5	28.6	33.3	37.2	45.5	43.4
Current smoker	25.9	24.8	15.6	12.8	6.6	6.3
Estrogen therapy use						
Past or current user	30.2	77.0	56.7	80.5	68.5	80.6
Duration of use (y)	4.8	4.4	3.2	2.6	5.7	7.8
Oral contraceptive use						
Past user	51.6	46.7	42.4	50.7	38.2	46.3
Duration of past use (y)	3.5	3.3	4.1	4.0	4.5	4.4
Parous	93.8	88.2	94.4	93.2	93.8	93.3
Parity‡	3.3	2.9	3.3	3.1	3.4	3.3
Physical activity (h/wk)	3.0	2.9	2.8	2.8	2.9	2.8
Alcohol						
Drinkers	59.3	52.7	56.6	57.3	51.9	53.0
Current drinkers (g/d)	9.4	8.8	9.6	9.1	8.7	10.2
Aspirin use						
Current user	35.5	33.5	33.6	34.5	32.4	34.6
Duration of use (y)	16.7	16.1	16.4	16.8	21.5	23.1

MI, myocardial infarction; BMI, body mass index.
Data are % unless otherwise specified.
* Data are means and percentages within the strata. Unless otherwise noted, data are from the 1980 questionnaire for women with prevalent hysterectomy or from the most recent questionnaire at the time of incident hysterectomy (1982–2006).
† Status reported in 1976 for women with prevalent hysterectomy or from the most recent questionnaire at the time of incident hysterectomy (1978–2006).
‡ Number of children among parous women.

for death from CHD, stroke, lung cancer, colorectal cancer, total cancers, and all-cause mortality did not demonstrate any age at which oophorectomy was associated with increased survival (Table 2).

For women younger than 50 years at the time of hysterectomy, bilateral oophorectomy was associated with significantly increased all-cause mortality in women who had never used estrogen therapy (HR 1.41, 95% CI 1.04 1.92, number needed to harm=8) but not in women who were past or current estrogen therapy users (HR 1.05, 95% CI 0.94–1.17). The results in these two categories of estrogen therapy use were statistically different ($P_{interaction}$=.03). A statistical difference in results by estrogen therapy use, with higher risk in the

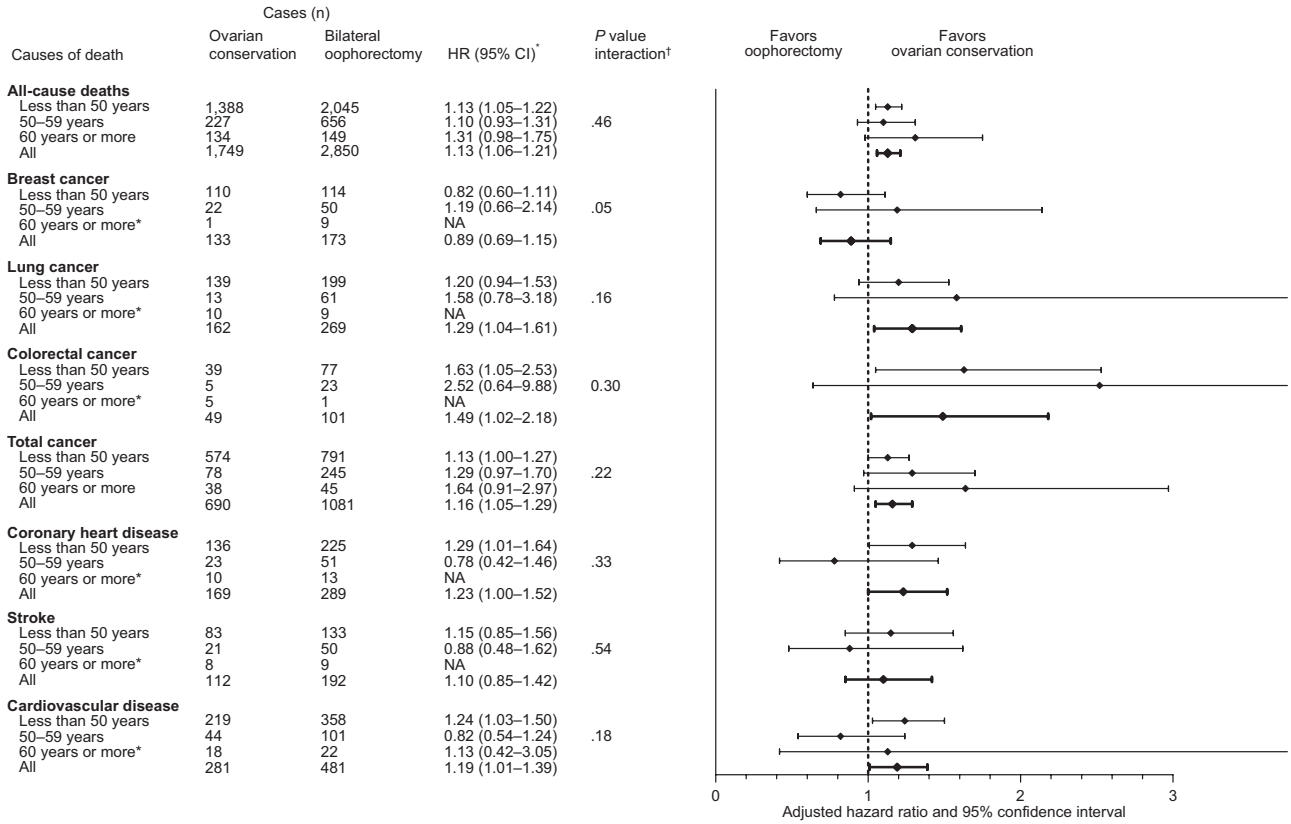

Fig. 1. Multivariable-adjusted risks of all-cause and cause-specific deaths for women with bilateral oophorectomy compared with ovarian conservation at time of hysterectomy stratified by age at hysterectomy. *All models were adjusted for age, age at hysterectomy, body mass index (BMI) in 1976, smoking status, use of estrogen therapy, past duration of oral contraceptive use, parity, physical activity, alcohol intake, and aspirin use. In addition, all-cause death models were adjusted for family history of myocardial infarction before age 60 years, tubal ligation, and family history of breast cancer; breast cancer models were adjusted for tubal ligation and family history of breast cancer; total cancer models were adjusted for tubal ligation; and coronary heart disease, stroke, and cardiovascular disease models were adjusted for family history of myocardial infarction before age 60 years. †*P* value for interaction between oophorectomy status and age at hysterectomy. The median year from study entry to all-cause death is 18.9 and 19.7 for women with ovarian conservation and both ovaries removed, respectively. The median year from study entry to all-cause death for all deceased women (n=4,599) is 19.4. HR, hazard ratio; CI, confidence interval; NA, not analyzed as a result of small numbers.

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never-users, was also observed for lung cancer mortality (HR 1.44, 95% CI 0.17–1.21, $P_{\text{interaction}}$=.02) and CHD mortality (HR 2.35, 95% CI 1.22–4.27; $P_{\text{interaction}}$=.02) (Fig. 2). Number need to harm for lung cancer deaths was 50 and for CHD deaths was 33.

In the 16,395 women who underwent hysterectomy after entering the cohort in 1976 and for whom cardiovascular disease risk factors were queried, oophorectomy was associated with an increased risk of cardiovascular disease mortality in the low-risk (HR 1.80, 95% CI 0.87–3.71) but not in the high-risk women (HR 0.90, 95% CI 0.59–1.38). However, power was low to determine that these risks were statistically different ($P_{\text{interaction}}$=.22). Results were similar for all-cause mortality. In other stratified analyses, all-cause mortality associated with oophorectomy did not differ by smoking status among all women in the study population. However, in the subgroup of women with oophorectomy before age 50 years who never used estrogen therapy, risk was highly elevated in the never-smokers (HR 3.09, 95% CI 1.38–6.44), moderately elevated in the former smokers (HR 1.83, 95% CI 0.93–3.59), and not elevated in the current smokers (HR 0.98, 95% CI 0.22–4.35) compared to women with ovarian conservation ($P_{\text{interaction}}$=.18). In a separate analysis, neither total mortality nor breast cancer mortality associated with oophorectomy differed for women with or without a family history of ovarian or breast cancer (in a mother or sister). However, our statistical power to evaluate mortality outcomes in high-risk women with a strong family history of these cancers was limited.

Table 2. Multivariable-Adjusted Analyses of All-Cause and Cause-Specific Mortality in Relation to Oophorectomy Status, Comparing Models Using Either Linear or Linear and Quadratic Terms for Age at Hysterectomy

	χ^2 Statistic*	*P*	Age at Hysterectomy at Which Oophorectomy Would Lower Risk
All-cause death	0.01	.915	
Breast cancer	3.90	.048	47.5
Lung cancer	0.79	.375	
Colorectal cancer	0.12	.724	
Total cancer	0.80	.372	
Coronary heart disease	1.73	.188	
Stroke	0.12	.727	

* From likelihood ratio test comparing linear with quadratic models.

To determine whether prolonged follow-up is needed to observe an increase in cardiovascular disease or all-cause mortality associated with bilateral oophorectomy, we examined women alive and free of cardiovascular disease 15 years after hysterectomy (n=23,244). Eighty percent of cardiovascular disease deaths and 80% of all deaths occurred 15 or more years after hysterectomy. For these women,

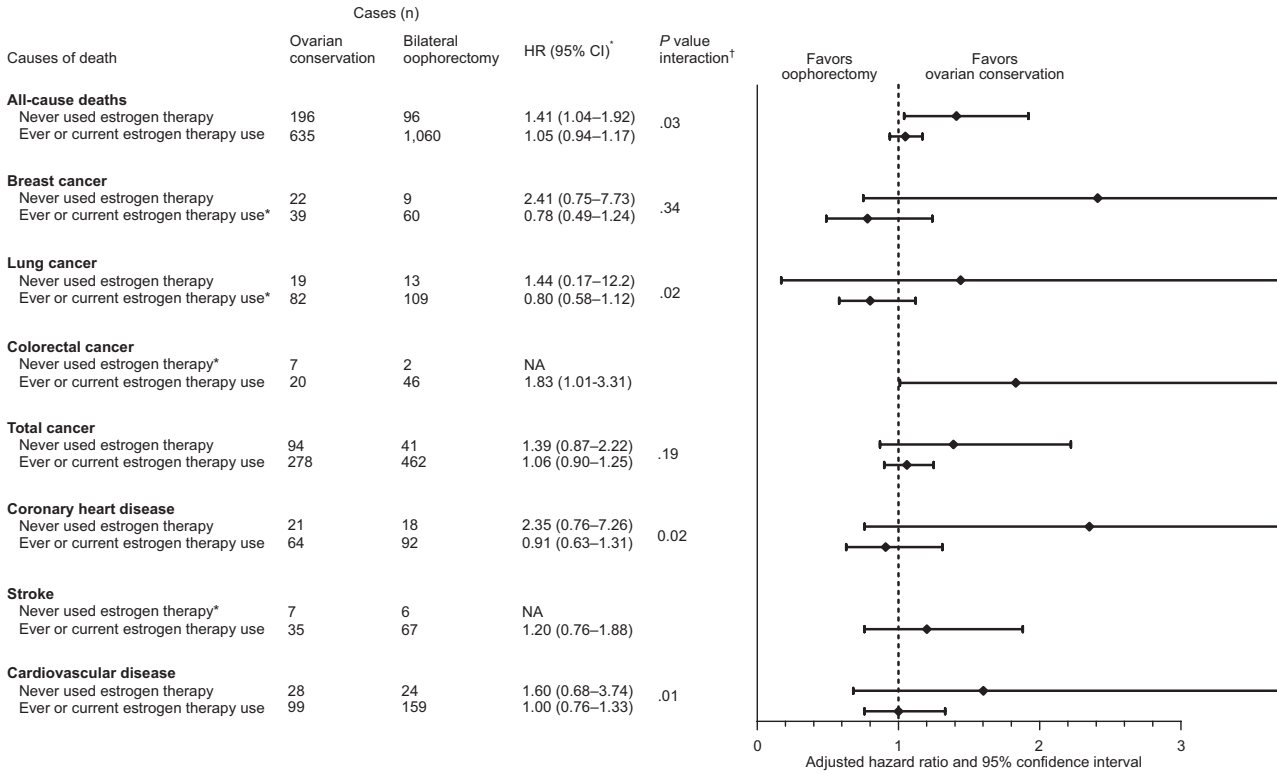

Fig. 2. Multivariable-adjusted risks of all-cause and cause-specific deaths for women with bilateral oophorectomy compared with ovarian conservation at time of hysterectomy before age 50 years stratified by use of estrogen therapy. *All models were adjusted for age, age at hysterectomy, body mass index (BMI) in 1976, smoking status, use of estrogen therapy, past duration of oral contraceptive use, parity, physical activity, alcohol intake, and aspirin use. In addition, all-cause death models were adjusted for family history of myocardial infarction before age 60 years, tubal ligation, and family history of breast cancer; breast cancer models were adjusted for tubal ligation and family history of breast cancer; total cancer models were adjusted for tubal ligation; and coronary heart disease, stroke, and cardiovascular disease models were adjusted for family †*P* value for interaction between oophorectomy status and use of estrogen therapy and history of myocardial infarction before age 60 years. HR, hazard ratio; CI, confidence interval; NA, not analyzed as a result of small numbers.

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oophorectomy was associated with a higher risk of death from all causes (HR 1.09, 95% CI 1.01–1.17) and cardiovascular disease (HR 1.14, 95% CI 0.95–1.37), similar to what was reported in Figure 1 for the full study population.

DISCUSSION

In this large, prospective cohort of over 30,000 women followed for 28 years, we found that at no age was there an overall survival benefit associated with bilateral oophorectomy compared with ovarian conservation at the time of hysterectomy for benign disease. Our analysis of the cohort, including 1,379 additional deaths subsequent to the 2009 Nurses' Health Study publication, found that at the time of hysterectomy, bilateral oophorectomy was associated with a marked reduction in mortality from ovarian cancer and a lower risk of mortality from breast cancer when oophorectomy was performed before age 47.5 years. Among the 30,117 study participants followed over 28 years, 44 women with ovarian conservation and four with oophorectomy died from ovarian cancer. However, these risks were overshadowed by the significantly increased risks of dying from other causes: a 23% increase in CHD mortality, a 29% increase in lung cancer mortality, a 49% increase in colorectal cancer mortality, and a 13% increase in all-cause mortality.

Additionally, we found that oophorectomy before age 50 years in women who never used estrogen therapy was associated with a 41% increased risk of all-cause mortality. Women who were past or current users of estrogen therapy did not demonstrate this increased risk. An analysis of the term of interaction confirmed these findings ($P_{\text{interaction}}=.03$). Lung cancer and cardiovascular disease mortality were also elevated only in the women who never used estrogen therapy. These findings suggest that estrogen therapy may ameliorate the increased mortality risks associated with bilateral oophorectomy in younger women.[12]

The finding that oophorectomy did not increase the risks of cardiovascular disease or all-cause mortality in women with known risk factors for cardiovascular disease was unexpected and suggests that oophorectomy may not modify the substantial risks these women already incur. However, oophorectomy did increase the risks of cardiovascular disease and all-cause mortality in low-risk women, suggesting that oophorectomy may have a greater effect on otherwise healthy women. Similarly, for women who never smoked and never used estrogen therapy, oophorectomy before age 50 years was associated with a 200% increase in mortality. We did not find this increased risk in current smokers, possibly because oophorectomy may not modify the established high risk of cardiovascular disease that is already present among smokers.

That oophorectomy may be associated with increased risk of colorectal cancer is biologically plausible. Estrogen receptors are present in human colorectal tissues and physiological levels of estrogen stimulate humoral and cell-mediated immune response.[13,14] We continue to find an association of oophorectomy with lung cancer in the Nurses' Health Study cohort. Although our earlier findings on oophorectomy and increased risk of incident lung cancer were unexpected, other studies subsequently found a similar association.[7,15,16] These observations that oophorectomy may affect lung cancer risk merit further investigation.

Our study has a number of strengths. The large size of our study cohort (30,117 women) and long-term follow-up (28 years) are important advantages over other observational studies. The finding in our study that 80% of both cardiovascular disease deaths and all deaths occurred 15 or more years after hysterectomy points out that prolonged follow-up is essential to observing the effect of oophorectomy on mortality. Study entry of our participants at young ages (range 30–55 years at Nurses' Health Study enrollment) took place many years before most of the deaths as a result of conditions of interest. Other strengths include our prospective cohort study design, very high follow-up rate, adjudicated and blinded assessment of all reported deaths, and multivariable analyses to correct for many known risk factors for the outcomes studied. Additionally, statistical differences between strata were assessed using the significance of interaction term ($P_{\text{interaction}}$), which considers the relationship among three or more variables when the simultaneous influence of two variables on a third is not additive.

We acknowledge several limitations of our study. The study is observational and the reasons why women chose oophorectomy or ovarian conservation or estrogen therapy use or no estrogen therapy use are not known. Differences in the use of medications such as statins, dietary factors, and environmental exposures may have differed by treatment group. However, most baseline characteristics were similar for the two groups, including many known risk factors for conditions studied. Lastly, our study population was mostly white and our findings may not apply to other ethnic groups.

Although our findings suggest that estrogen therapy ameliorates the elevated risks of all-cause and cardiovascular disease mortality associated with

oophorectomy before age 50 years, the number of women currently taking estrogen continues to decline after the Women's Health Initiative.[17] Therefore, a strategy of performing oophorectomy and prescribing estrogen after surgery is not likely to be successful. Although challenging, a prospective trial, randomized to oophorectomy or ovarian conservation with prolonged follow-up, is needed to confirm our findings. Lacking such a trial, high-quality observational studies provide a valuable method to evaluate these associations.

At the time of hysterectomy, women with known high-penetrance susceptibility genes for ovarian and breast cancer (*BRCA*, Lynch) should strongly consider oophorectomy because the lifetime risk of ovarian cancer is high.[18] In contrast, approximately 300,000 U.S. women without these mutations, and many more worldwide, have bilateral oophorectomy at the time of hysterectomy for benign disease every year. Consequently, the association of oophorectomy with increased mortality in the overall population has substantial public health implications.

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