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Bilateral oophorectomy is not associated with increased mortality: the California Teachers Study

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Abstract

Objective—To investigate the effect of surgical menopause due to bilateral oophorectomy on mortality, in light of evidence that bilateral oophorectomy among premenopausal women rapidly reduces endogenous hormone levels thereby modifying risks of cardiovascular disease and breast cancer.

Design—The California Teachers Study (CTS) is a prospective cohort study of 133,479 women initiated in 1995–1996 through a mailed, self-administered questionnaire. Relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression.

Subjects—CTS participants who, at baseline, reported having surgical menopause due to bilateral oophorectomy (n=9,785), were compared to participants with natural menopause (n=32,219).

Main outcome measures—We investigated whether bilateral oophorectomy was associated with all-cause, cardiovascular, or cancer mortality, overall and by menopausal hormone therapy (HT) use status.

Results—Among participants younger than 45 years of age at menopause, multivariable relative risks were 0.86 (95% CI, 0.74–1.00), 0.85 (95% CI, 0.66–1.11) and 0.91 (95% CI, 0.67–1.23) for

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all-cause mortality, cardiovascular mortality and cancer mortality, respectively. Among participants with an age at menopause of 45 years or later, multivariable relative risks were 0.87 (95% CI, 0.80–0.94), 0.83 (95% CI, 0.71–0.96) and 0.84 (95% CI, 0.72–0.98) for all-cause, cardiovascular and cancer mortality, respectively. The association between bilateral oophorectomy and mortality did not differ by baseline status of HT use.

Conclusions—Surgical menopause due to bilateral oophorectomy vs. natural menopause does not increase all-cause, cardiovascular, or cancer mortality.

Keywords

surgical menopause and mortality; bilateral oophorectomy; mortality; California Teachers Study

INTRODUCTION

In the United States between 2000 and 2004, approximately 600,000 women underwent a hysterectomy annually (1). The most frequent indications for hysterectomy were uterine leiomyoma and endometriosis and approximately 54% of hysterectomies were performed with a concurrent bilateral oophorectomy (1). Long-term survival benefits appear to outweigh risks for women who undergo elective prophylactic bilateral oophorectomy after age 65 (2), but the mortality effects of surgical menopause at younger ages are uncertain. The complete elimination of ovarian hormone production with no estrogen supplementation after oophorectomy appears to increase the risk of incident and fatal cardiovascular disease, compared with the expected risks among women without oophorectomy whose ovaries continue to produce endogenous hormones up to the time of natural menopause.

One goal of prescribing menopausal hormone therapy (HT) to women after bilateral oophorectomy has been to “replace” those lost endogenous hormones; prior studies have shown that HT use is associated with reduced mortality (3–6), including a recent analysis within the CTS which showed an association between HT use and reduced mortality among younger but not older postmenopausal participants (7). Despite large numbers of women who have undergone bilateral oophorectomy and used HT, most of whom used estrogen therapy (ET) because of a concurrent hysterectomy, the net effects of surgical menopause due to bilateral oophorectomy and HT use on overall mortality are unclear. A prospective cohort study conducted within the Mayo Clinic (Minnesota) patient population reported that, while mortality was not increased in women who underwent a bilateral oophorectomy compared with women who did not undergo oophorectomy overall, increased mortalities were observed among women who had the surgery before the age of 45 years (8). Results from a large prospective cohort study of nurses suggested that hysterectomy plus bilateral oophorectomy, compared with simple hysterectomy, was associated with increased total mortality and mortality due to coronary heart disease and all cancers (9).

We used data from the California Teachers Study (CTS), an ongoing prospective cohort, to examine whether all-cause mortality, cardiovascular-specific mortality or cancer-specific mortality were higher among premenopausal participants who became menopausal due to a bilateral oophorectomy compared to participants who experienced natural menopause.

MATERIALS AND METHODS

Study design and data collection

A detailed description of the CTS population and study design has been published (10). 133,479 female current or former California teachers and administrators returned the baseline mailed questionnaire and were thereby enrolled in the CTS in 1995–1996. The CTS

is followed annually for incident cancers via linkage with the population-based statewide California Cancer Registry and for mortality outcomes via linkage with the California Automated Mortality Linkage System, the Social Security Administration Death Master File and the National Death Index. Causes of death are taken from the underlying causes recorded on the death certificate and, for out-of-state deaths, were obtained from the National Death Index. The CTS is also linked annually with the hospital discharge database for California that is compiled by the Office of Statewide Health Planning and Development (OSHPD). Use of data for analyses was approved by the Institutional Review Boards at each collaborating institution in accord with assurances approved by the United States Department of Health and Human Services. None of the authors have any financial disclosure to make or potential conflicts of interest to declare.

The self-administered baseline questionnaire collected demographic and exposure information for this analysis. Participants were classified as postmenopausal if they met any of the following criteria: 1) periods stopped more than 6 months ago, 2) bilateral oophorectomy, 3) age 56 years or older at baseline and not already classified as premenopausal or perimenopausal, 4) initiated HT for menopausal symptoms before periods stopped, or 5) hysterectomy before age 56 years but aged 56 years or older at baseline. The baseline questionnaire ascertained both oophorectomy status, including extent of (partial, unilateral, or bilateral) and age at surgery (in categories); hysterectomy status and age at surgery (in categories). Participants were not asked whether the fallopian tubes were removed at the time of oophorectomy, nor indication for oophorectomy. Other factors such as race, detailed HT use (e.g., formulation, duration, and ages of use), personal health history, smoking history, and body mass index (BMI, kg/m^2) were also collected.

The current analysis was restricted to eligible postmenopausal participants whose menopause was either natural or due to surgery (bilateral oophorectomy). From the entire cohort of 133,479 participants, the following exclusions were made in order: 66 participants who lived outside the United States at baseline (because mortality linkages would not identify deaths among this group); 22 participants who requested being included only in breast cancer research projects; 2,603 participants with missing data on history of cancer or other medical conditions, menopausal status, or gynecologic surgery. Of the remaining CTS participants, 52,446 had either natural menopause or menopause due to bilateral oophorectomy. We then excluded 5,954 participants who reported a personal history of breast, ovarian, endometrial, or cervical cancer at baseline (because oophorectomy among these participants would likely have been therapeutic rather than prophylactic); 1,502 participants who were 85 years or older at baseline, and 2,986 participants whose HT use was unknown. A total of 42,004 CTS participants were included in the overall analysis.

For categorization of primary exposure, 32,219 participants who reported that their periods had stopped naturally more than 6 months prior to submitting the baseline questionnaire were classified as postmenopausal due to natural menopause. This group of participants with a natural menopause was the reference group, or non-exposed group, for the primary exposure of interest in this analysis. 9,785 participants who reported that their periods had stopped due to surgery and that they had had both ovaries removed were classified as postmenopausal due to bilateral oophorectomy. This group of participants with a bilateral oophorectomy as the cause of menopause was the exposed group for the primary exposure of interest in this analysis.

To assess the validity of self-reported gynecological surgery status among the exposed group we compared information on gynecological surgeries recorded in the OSHPD hospital discharge database to participant reports in the baseline questionnaire. The first year for which OSHPD data were available was 1991. Among 2,123 participants identified in the

OSHPD database as having had a bilateral oophorectomy between 1991 and baseline (1995–1996), 97% reported having had a bilateral oophorectomy on the baseline questionnaire. Among 1,674 CTS participants who reported having had a bilateral oophorectomy before periods stopped on the baseline questionnaire, for whom OSHPD data were available, the age at gynecologic surgery reported in OSHPD fell within the self-reported categorical age at gynecologic surgery. Among the 8% discordant for age at surgery, 86% differed by one age category (age at oophorectomy was categorized as <25, 25–34, 35–44, 45–49, 50–54, 55–59, 60–64, and 65+ years old). Among 3,249 participants with a hysterectomy reported in OSHPD between 1991 and baseline, hysterectomy was reported on the baseline questionnaire by 99.7% of the participants.

Our main analytic endpoints were all-cause mortality and two types of cause-specific mortality. Mortality due to cardiovascular disease was based on cause of death attributed to ICD-9 codes 390–459 (diseases of the circulatory system) or 745–747 (anomalies of the cardiovascular system), or ICD-10 codes I (diseases of the circulatory system) and Q20–28 (anomalies of the cardiovascular system). Mortality due to cancer was based on cause of death attributed to ICD-9 codes 140–208 (neoplasms) and ICD-10 code C (neoplasms). Analyses of cause-specific mortality excluded 419 participants with unknown cause of death.

Statistical Analysis

Baseline characteristics by type of menopause (surgical due to bilateral oophorectomy vs. natural) were compared using the Chi-square test. Multivariable Cox proportional hazards regression models, with age (in days) as the time scale, provided estimates of the relative risks (RR) and the 95% confidence intervals (CI) for all-cause mortality, cardiovascular mortality and cancer mortality. Participants were followed from cohort entry until the first of the following events: death, move out of the United States, or end of follow-up period, which was December 31, 2007. The models for all-cause mortality were adjusted for baseline, self-reported measures of body mass index (16–24.9, 25–29.9, 30–54.9 kg/m2 and unknown), race (white, African American, other), smoking history (never smoker, former smoker, current smoker), prior history of diabetes (yes or no), prior history of high blood pressure (yes or no), prior history of heart attack/myocardial infarction (yes or no) and prior history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no). The model with all participants was additionally adjusted for age at exposure (natural menopause or bilateral oophorectomy). The models for cardiovascular mortality were configured in the same manner as described above for all-cause mortality, except they were not adjusted for prior history of heart attack/myocardial infarction. The models for cancer mortality were configured in the same manner as described above for all-cause mortality, except that they were not adjusted for prior personal history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no), and they were additionally adjusted for family history of at least one of the following cancers (breast, endometrium, ovary, cervix, lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, prostate, thyroid or melanoma, yes/no).All Cox models were fit using the PHREG procedure in SAS version 9.2 (SAS Institute, Cary, North Carolina). In light of the long follow-up period in consideration the STRATA=VARIABLE statement in the PHREG procedure was used to adjust for any cohort effect; the variable was set to age (in years) at cohort entry, a proxy for birth year. The use of age at cohort entry in years vs. use of a categorical variable for age at cohort entry (ie. 5-year intervals) in the STRATA statement ensures that any effect of a single important publication or event would be adjusted for and is made possible because of the large sample size of the CTS.

Because many women who undergo surgical menopause due to bilateral oophorectomy begin HT use shortly thereafter, we also performed a stratified analyses based on HT use (ever vs. never) at baseline. Ever-users were further stratified by formulation [ET only vs. estrogen plus progestin therapy (EPT) only] in analyses that excluded participants who used more than one formulation. Models were also stratified by age at natural/surgical menopause (before age 45 years vs. 45+ years) to subset the participants with surgical menopause due to bilateral oophorectomy at a younger age. For all models, two-sided *p* values of less than 0.05 were considered to be statistically significant.

RESULTS

Most participants included in these analyses were white and were never smokers (Table 1). The proportion of ever HT users differed by primary exposure status (bilateral oophorectomy vs. natural menopause), at 96.8% among participants with bilateral oophorectomy and 66.3% among participants with natural menopause. Compared to participants with natural menopause, participants with a bilateral oophorectomy had a higher BMI, were more likely to be African American, had higher prevalence of high blood pressure, were more likely to have a family history of breast, ovarian, endometrial or cervical cancer, and were less likely to have a history of heart attack or myocardial infarction.

A total of 6,032 deaths occurred during an overall average follow-up of 11.3 years (Table 1); 1,028 deaths (17.0%) occurred among participants who reported a surgical menopause due to bilateral oophorectomy. Cardiovascular mortality and cancer mortality accounted for 2,067 (34.3%) and 1,754 (29.1%) deaths, respectively.

Having a surgical menopause due to bilateral oophorectomy, vs. having a natural menopause, was not associated with increased mortality in the CTS. For participants younger than 45 years of age at menopause, multivariable relative risks were 0.86 (95% CI, 0.74–1.00), 0.85 (95% CI, 0.66–1.11) and 0.91 (95% CI, 0.67–1.23) for all-cause mortality, cardiovascular mortality and cancer mortality, respectively (Table 2). For participants who were at least 45 years of age at menopause, bilateral oophorectomy was marginally associated with decreased all-cause mortality (RR, 0.87; 95% CI, 0.80–0.94), cardiovascular mortality (RR, 0.83; 95% CI, 0.71–0.96) and cancer mortality (RR, 0.84; 95% CI, 0.72–0.98).

Bilateral oophorectomy did not appear to confer mortality protection independent of that provided by HT use. Among women of all ages combined, using natural menopause and never use of HT as the reference group, bilateral oophorectomy in never HT users was not statistically significantly associated with all-cause mortality (RR, 0.94; 95% CI, 0.76–1.16), cardiovascular mortality (RR, 0.95; 95% CI, 0.69–1.31) or cancer mortality (RR, 0.89; 95% CI, 0.55–1.45). The relative risks for bilateral oophorectomy in ever HT users were 0.79 (95% CI, 0.73–0.86) for allcause mortality, 0.77 (95% CI, 0.67–0.88) for cardiovascular mortality and 0.78 (95% CI, 0.67–0.90) for cancer mortality. Stratification by age at menopause (<45 vs. ≥45), did not change these results markedly. Investigation of the association between primary exposure status (surgical menopause due to bilateral oophorectomy vs. natural menopause) and mortality by HT formulation showed no clear statistically significant differences by formulation (Table 3).

In several additional analyses we assessed whether results were dependent on the definition of reference group. In one such analysis we excluded participants who reported experiencing a natural menopause but who had a hysterectomy at a later date (n=3,815). Results did not differ significantly from those presented and are thus not shown.

DISCUSSION

Several previous studies have suggested that bilateral oophorectomy may confer increased mortality risk. In the CTS, surgical menopause due to bilateral oophorectomy does not confer increased mortality over natural menopause.

Previously published results from a large prospective cohort of nurses showed that bilateral oophorectomy concurrent with hysterectomy vs. hysterectomy alone, conferred increases in total mortality, fatal plus nonfatal coronary heart disease mortality as well as mortality due to all cancers; however risks of breast cancer, ovarian cancer and total cancer were decreased (9). The prior analysis appeared to include oophorectomy procedures before, during and after menopause. Our CTS analysis compared mortality among premenopausal women who underwent oophorectomy with mortality among women who experienced natural menopause. Thus, the two studies address similar yet importantly different research questions.

Another prospective study, comparing women with a bilateral oophorectomy to referent women of similar age with intact ovaries showed that overall mortality was not increased among all women, but was increased among the small group of women who had the bilateral oophorectomy before age 45 years, and particularly among the women who did not use any estrogen therapy up to age 45 (8). Since the number of women who undergo surgical menopause at a younger age and do not take some form of HT is small, the generalizability of this finding is uncertain. We did not observe increased mortality in the younger age stratum.

Prior epidemiologic studies have shown that HT use is associated with reduced mortality (3–6), including a recent analysis within the CTS which showed an association between HT use and reduced mortality that diminished with increasing age (7). We observed a marginally decreased risk of all-cause mortality among ever HT users who had a surgical menopause due to bilateral oophorectomy, however we observed no statistically significant association between bilateral oophorectomy and mortality among never HT users, suggesting that the decreased mortality observed in the HT users is not driven by the surgery.

Strengths of the current report include the depth of data on exposure and covariates. The CTS baseline questionnaire captured detailed information about age at and type of menopause, allowing the investigators to evaluate the impact of bilateral oophorectomy as the cause of menopause compared to natural menopause on mortality. Use of the OSHPD data allowed for assessment of the validity of self-reported gynecologic surgery information on a subset of participants for whom OSHPD data were available, an assessment which showed excellent agreement between self-reported and OSHPD-derived surgery status. Outcome ascertainment was achieved by use of three sources of information on deaths, including the California Automated Mortality Linkage System, the Social Security Administration Death Master File and the National Death Index.

The present study has several limitations. First, the prospective follow-up period of approximately 10 years may appear to be too short to provide definitive data on long-term risks of mortality after bilateral oophorectomy, however participants were retrospectively reporting these surgeries and thus technically the follow-up time was much longer than 10 years. In fact many participants had the surgery more than 10 years before they enrolled in the CTS. This design does however introduce a potential bias away from the null if the proportion of women with a bilateral oophorectomy who died and therefore could not be enrolled in the CTS was greater than the proportion of women with no bilateral oophorectomy who died and were therefore not enrolled. Such a scenario might be predicted to exaggerate the inverse association between bilateral oophorectomy and mortality.

Although we attempted to isolate surgeries that were likely to be prophylactic by excluding participants with a personal history of breast, ovarian, endometrial, or cervical cancer at baseline, and additionally stratifying by age at menopause, the lack of information in the CTS on reason for bilateral oophorectomy limited our ability to further differentiate surgeries performed solely for prophylactic removal of the ovaries from those performed during gynecologic surgery for a benign tumor or for non-gynecological problems (11). Some previous studies have included indication for surgery, but there remains a potential for confounding by indication in the other studies that, like ours, did not assess specific reasons for surgeries. Another limitation stems from the fact that the variable for age at menopause in the CTS was categorical, which precludes control for age at menopause in individual years. However women often do not remember the exact year of menopause and thus it is considered appropriate to analyze age at menopause as a categorical variable. The small number of participants in certain sub-groups, such as participants with a surgical menopause due to bilateral oophorectomy who had never used HT, limits power to detect differences in these groups.

The final limitation is relevant to the decision to include participants with self-reported prior histories of heart attack/myocardial infarction and prior cancer diagnoses in the models for cardiovascular mortality and cancer mortality, respectively. While the baseline questionnaire did assess prior history of heart attack/myocardial infarction and prior cancer diagnoses, it did not ask for timing of such prior events, thereby precluding the comparison of prior histories to timing of menopause. Neither exclusion of participants with baseline, self-reported prior histories of heart attack/myocardial infarction from the cardiovascular mortality models, nor exclusion of participants with a baseline, self-reported prior history of at least one of the following cancers (lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma) from the cancer mortality models altered the results from those shown.

The present study does not support the hypothesis that bilateral oophorectomy is associated with increased mortality.

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Table 1

Baseline characteristics of 42,004 California Teachers Study participants with natural menopause or bilateral oophorectomy, by baseline status of menopausal hormone therapy (HT) use, 1995–2007

	Natural Menopause		Bilateral Oophorectomy	
	Never HT users	**Ever HT users**	**Never HT users**	**Ever HT users**
Number	10,851	21,368	309	9,476
Average age at baseline (y) (SD)	65.4 (9.3)	62.7 (9.0)	67.9 (10.4)	59.2 (9.8)
Average follow-up time (y) (SD)	11.0 (2.4)	11.4 (2.0)	10.5 (2.8)	11.5 (1.7)
Deaths due to all causes (N)	2,183	2,821	92	936
Deaths due to cardiovascular disease (N)	800	929	40	298
Deaths due to cancer (N)	529	769	16	235
Age at menopause (natural menopause or due to bilateral oophorectomy) (y) (%)				
< 45	7.9	7.6	43.4	38.2
45 – 49	31.2	31.4	33.0	38.7
≥50	61.0	61.0	23.6	23.1
BMI, kg/ m^2 (%)[a]				
16 – 24.9	48.1	57.4	41.8	50.9
25 – 29.9	26.9	26.5	29.5	27.6
30 – 54.9	17.1	11.6	22.0	17.0
Race (%)				
White	86.8	91.5	82.2	88.6
African American	4.2	1.8	8.1	3.6
Other[b]	9.0	6.7	9.7	7.8
Smoking (%)[a]				
Never smoker	60.5	56.0	59.9	61.2
Former smoker	30.5	37.3	30.4	33.1
Current smoker	8.5	6.2	8.7	5.1
Family history of cancer (%)				
Breast cancer	15.3	13.0	14.6	13.6
Ovarian cancer	2.8	2.5	3.7	3.6
Endometrial cancer	3.0	3.3	3.6	4.1
Cervical cancer	2.9	2.9	2.9	3.2
Personal health history (%)				
Diabetes	5.2	3.1	9.4	3.4
Heart attack/Myocardial infarction	2.4	1.8	3.9	1.6
High blood pressure	26.3	23.2	37.2	27.9
Cancer[c]	3.9	3.6	10.0	4.0

[a] Participants with out of range or unknown values are not shown in the table.

[b] Includes Hispanic, Native American, Asian /Pacific islander, none reported or mixed.

[c] Ever diagnosed with one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid or melanoma. By design, study excludes women reporting breast, endometrial, ovarian or cervical cancer at baseline.

Table 2

Relative risks (RR) and 95% confidence intervals (CI) of all-cause and cause-specific mortality, overall and by age at natural menopause or age at bilateral oophorectomy in 42,004 participants in the California Teachers Study, 1995–2007

	All		Age at natural menopause or age at bilateral oophorectomy			
			<45 years		≥45 years	
	Deaths	RR (95% CI)	Deaths	RR (95% CI)	Deaths	RR (95% CI)
All-cause mortality						
Natural menopause	5,004	1.00	442	1.00	4,562	1.00
Bilateral oophorectomy[a]	1,028	0.87 (0.81 – 0.94)	384	0.86 (0.74 – 1.00)	644	0.87 (0.80 – 0.94)
Natural menopause, never HT user	2,183	1.00	213	1.00	1,970	1.00
Natural menopause, ever HT user[a]	2,821	0.87 (0.82 – 0.92)	229	0.90 (0.74 – 1.09)	2,592	0.86 (0.81 – 0.92)
Bilateral oophorectomy, never HT user[a]	92	0.94 (0.76 – 1.16)	47	0.96 (0.69 – 1.34)	45	0.90 (0.67 – 1.21)
Bilateral oophorectomy, ever HT user[a]	936	0.79 (0.73 – 0.86)	337	0.79 (0.66 – 0.95)	599	0.79 (0.72 – 0.86)
Cardiovascular mortality						
Natural menopause	1,729	1.00	157	1.00	1,572	1.00
Bilateral oophorectomy[b]	338	0.86 (0.76 – 0.97)	136	0.85 (0.66 – 1.11)	202	0.83 (0.71 – 0.96)
Natural menopause, never HT user	800	1.00	80	1.00	720	1.00
Natural menopause, ever HT user[a]	929	0.85 (0.77 – 0.94)	77	0.91 (0.66 – 1.25)	852	0.85 (0.76 – 0.94)
Bilateral oophorectomy, never HT user[b]	40	0.95 (0.69 – 1.31)	24	1.16 (0.71 – 1.89)	16	0.74 (0.45 – 1.22)
Bilateral oophorectomy, ever HT user[a]	298	0.77 (0.67 – 0.88)	112	0.77 (0.56 – 1.05)	186	0.75 (0.64 – 0.88)
Cancer mortality						
Natural menopause	1,461	1.00	100	1.00	1,361	1.00
Bilateral oophorectomy[c]	293	0.85 (0.74–0.97)	97	0.91 (0.67–1.23)	196	0.84 (0.72–0.98)
Natural menopause, never HT user	589	1.00	44	1.00	545	1.00
Natural menopause, ever HT user[c]	872	0.88 (0.79–0.97)	56	0.91 (0.60–1.36)	816	0.87 (0.78–0.97)
Bilateral oophorectomy, never HT user[c]	17	0.89 (0.55–1.45)	4	0.54 (0.19–1.54)	13	1.16 (0.67–2.02)
Bilateral oophorectomy, ever HT user[c]	276	0.78 (0.67–0.90)	93	0.88 (0.60–1.29)	183	0.75 (0.63–0.89)

[a] Adjusted for baseline self-reported measures of body mass index (16–24.9, 25–29.9, 30–54.9 kg/m2 and unknown), race (white, African American, other), smoking history (never smoker, former smoker, current smoker), prior history of diabetes (yes or no), prior history of high blood pressure (yes or no), prior history of heart attack/myocardial infarction (yes or no) and prior history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no). The STRATA=VARIABLE statement was used, in which the variable was set to the age in years at cohort entry to adjust for any cohort effect. Model with all participants additionally adjusted for age at exposure (natural menopause or bilateral oophorectomy).

[b] Same as for 'a' except not adjusted for prior history of heart attack/myocardial infarction.

[c] Same as for 'a' except not adjusted for prior personal history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no), and additionally adjusted for family history of at least one of the following cancers (breast, endometrium, ovary, cervix, lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, prostate, thyroid or melanoma, yes/ no).

Participants with out of range or unknown values are not shown in the table.

Table 3

Relative risks (RR) and 95% confidence intervals (CI) of all-cause and cause-specific mortality by ever use of menopausal hormone therapy (HT) in the form of estrogen therapy (ET) or estrogen plus progestin therapy (EPT), overall and by age at natural menopause or age at bilateral oophorectomy in 42,004 California Teachers Study participants, 1995–2007

	All		Age at natural menopause or age at bilateral oophorectomy			
			<45 years		≥45 years	
	Deaths	RR (95% CI)	Deaths	RR (95% CI)	Deaths	RR (95% CI)
All-cause mortality						
Natural menopause, never HT user	2,183	1.00	213	1.00	1,970	1.00
Natural menopause, ever HT user of ET only[a]	1,297	0.94 (0.88 – 1.01)	123	1.02 (0.81 – 1.28)	1,174	0.93 (0.87 – 1.00)
Natural menopause, ever HT user of EPT only[a]	908	0.78 (0.72 – 0.85)	51	0.69 (0.50 – 0.95)	857	0.79 (0.72 – 0.86)
Bilateral oophorectomy, ever HT user of ET only[a]	774	0.82 (0.75 – 0.89)	288	0.83 (0.68 – 1.00)	486	0.80 (0.72–0.88)
Bilateral oophorectomy, ever HT user of EPT only[a]	19	0.54 (0.34 – 0.85)	3	0.23 (0.07 – 0.71)	16	0.70 (0.43 – 1.16)
Cardiovascular mortality						
Natural menopause, never HT user	800	1.00	80	1.00	720	1.00
Natural menopause, ever HT user of ET only[b]	504	0.93 (0.83 – 1.04)	48	1.12 (0.77 – 1.62)	456	0.90 (0.80 – 1.01)
Natural menopause, ever HT user of EPT only[b]	220	0.72 (0.61 – 0.84)	12	0.56 (0.30 – 1.05)	208	0.74 (0.62 – 0.87)
Bilateral oophorectomy, ever HT user of ET only[b]	259	0.80 (0.69 – 0.93)	100	0.81 (0.59 – 1.11)	159	0.77 (0.65 – 0.92)
Bilateral oophorectomy, ever HT user of EPT only[b]	4	0.44 (0.17 – 1.19)	1	0.25 (0.03 – 1.83)	3	0.56 (0.18 – 1.74)
Cancer mortality						
Natural menopause, never HT user	589	1.00	44	1.00	545	1.00
Natural menopause, ever HT user of ET only[c]	310	1.00 (0.87–1.15)	26	1.08 (0.66–1.77)	284	0.99 (0.86–1.15)
Natural menopause, ever HT user of EPT only[c]	374	0.79 (0.69–0.91)	13	0.56 (0.29–1.06)	361	0.80 (0.70–0.92)
Bilateral oophorectomy, ever HT user of ET only[c]	209	0.77 (0.65–0.91)	75	0.90 (0.60–1.33)	134	0.72 (0.60–0.88)
Bilateral oophorectomy, ever HT user of EPT only[c]	9	0.62 (0.32–1.21)	0	NA	9	0.87 (0.45–1.70)

[a] Adjusted for baseline self-reported measures of body mass index (16–24.9, 25–29.9, 30–54.9 kg/m2 and unknown), race (white, African American, other), smoking history (never smoker, former smoker, current smoker), prior history of diabetes (yes or no), prior history of high blood pressure (yes or no), prior history of heart attack/myocardial infarction (yes or no) and prior history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no). The STRATA=VARIABLE statement was used, in which the variable was set to the age in years at cohort entry to adjust for any cohort effect. Model with all participants additionally adjusted for age at exposure (natural menopause or bilateral oophorectomy).

[b] Same as for 'a' except not adjusted for prior history of heart attack/myocardial infarction.

[c] Same as for 'a' except not adjusted for prior personal history of at least one of the following cancers: lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, thyroid and melanoma (yes or no), and additionally adjusted for family history of at least one of the following cancers (breast, endometrium, ovary, cervix, lung, leukemia, Hodgkin's lymphoma, other lymphoma, colorectal, prostate, thyroid or melanoma, yes/ no).

Participants with out of range or unknown values are not shown in the table.