Published in final edited form as:
Menopause. 2011 March ; 18(3): 253–261. doi:10.1097/gme.0b013e3181f0839a.

Age-specific effects of hormone therapy use on overall mortality and ischemic heart disease mortality among women in the California Teachers Study

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Abstract

Objective—Although the Women's Health Initiative trial (WHI) suggested that menopausal hormone therapy (HT) does not reduce coronary heart disease mortality overall, subsequent results have suggested that there may be a benefit in younger women. The California Teachers Cohort Study (CTS) questionnaire and mortality data was used to examine whether age modified the association between HT and the relative risk of overall mortality and ischemic heart disease (IHD) deaths.

Methods—Participants from the CTS were 71,237 postmenopausal women (mean age = 63, range 36 to 94 years) followed prospectively for mortality and other outcomes from 1995–1996 through 2004.

Results—Age at baseline was a much more important modifier of HT effects than age at start of therapy. Risks for all-cause mortality (n=8,399) were lower for younger current HT users at baseline than for never users (for women ≤60 years: HR=0.54, 95% CI=0.46–0.62). These risk reductions greatly diminished, in a roughly linear fashion, with increasing baseline age (for women 85–94 years HR=0.94, 95% CI=0.81–1.10 for all-cause mortality). Similar results were seen for IHD deaths (n=1,464). No additional significant modifying effects of age at first use, duration of use, or formulation were apparent.

Conclusions—These results provide evidence that reduced risks of mortality associated with HT use are observed among younger users but not for older postmenopausal women even those starting therapy close to their time of menopause.

Keywords

Overall mortality; heart disease; menopausal hormone therapy; risk; survival; age

Introduction

Numerous observational studies have suggested an inverse association between menopausal hormone therapy (HT) containing estrogen (ET) or combined estrogen and progestin (EPT) and incidence or death from coronary heart disease(CHD). A 1998 meta-analysis of 25 observational studies reported a 30% lower risk of CHD in estrogen therapy (ET) users and a 34% lower risk in combined estrogen and progestin therapy (EPT) users compared to nonusers [1]. Both current (versus former) use and longer duration of use [2] have been associated with reduced CHD risk. Several biological mechanisms have been proposed for the protective effects of estrogen on CHD risk; the most widely recognized are favorable changes in circulating levels of the lipoproteins LDL and HDL [3–5]. Observational studies have also reported 20–45% decreased risk of all-cause mortality, consisting largely of reductions in cardiovascular mortality among HT users compared to nonusers [2–4,6].

However, in contrast to the above, randomized clinical trials have shown no benefit or even an increased risk of CHD incidence with current use of ET or EPT [5,7]. A meta-analysis of 22 small clinical trials [8], the Heart and Estrogen-Progestin Replacement Study [7] and the Women's Health Initiative (WHI) [5,9] reported no difference in risk of CHD death between women randomized to HT and those randomized to placebo. Analysis of overall mortality in the WHI [10] also found no benefit of ET or EPT therapy.

It has been suspected that the time when a woman begins HT therapy, i.e. her age or the time duration since her menopause, plays a role in the apparent discrepancies between observational study results and those of randomized trials, such as the WHI, with regard to the benefits of HT therapy on CHD incidence or mortality [10,11]. Two re-analyses of the Nurses' Health Study data [12,13] have indicated that any benefit of HT therapy on cardiovascular disease is restricted to women who started therapy within 10 years of menopause. Moreover age at HT randomization appears to modify the effect of HT on risks of overall mortality and CHD incidence [10] in the WHI data as well, and women aged 50–59 years when randomized to HT had a reduced risk of mortality overall.

Given these differing findings by age at treatment, we sought to clarify the joint effect of HT and age on all-cause and CHD mortality in the large, prospective California Teachers Study (CTS) cohort [14]. We focused specifically on ischemic heart disease (IHD) deaths which are, by far, the largest contributor to CHD mortality in the United States and examined age at current use, prior use, duration of use, and age at first use as modifier of HT effects on risk of these events.

Methods

Study population

A detailed description of the CTS has been published previously [14]. Briefly, the CTS is a prospective cohort study of 133,479 current and retired female public school teachers and administrators who participated in the California State Teachers Retirement System and returned a mailed, self-administered questionnaire in 1995–1996. The baseline questionnaire obtained information on menstrual and reproductive events, use of HT and oral contraceptives, family and personal history of diseases, physical activity, smoking, diet and alcohol consumption; a validation/calibration study [15] found reasonable agreement between dietary variables measured using the baseline questionnaire and 24 hour recalls for a subsample of the cohort. The study was approved by the Institutional Review Boards at all collaborating institutions.

For this analysis, we determined menopausal status based on the first questionnaire self-reports of natural or surgical menopause for all CTS participants. After excluding all women who were premenopausal or of unknown menopausal status, we also excluded women who reported a hysterectomy with at least part of an ovary left intact and who were less than 56 years old at baseline. This yielded 77,890 post-menopausal women. From this analytic cohort, we excluded women with incomplete information on ever use of HT (n=6,004), women older than 94 years at baseline (n=75), and women with missing data on smoking status (n=480). We also excluded (n=94) women who, while meeting all the above requirements, were 36 years of age or less at baseline, leaving 71,237 postmenopausal women for analysis.

Follow-up and outcomes

Women contributed person-days of follow-up beginning on the date they completed the baseline questionnaire and continued until either their date of death or December 31, 2004, whichever occurred earlier. Deaths were identified by annual linkage with California mortality files and the Social Security Administration death file. Cause of death was obtained from the California mortality files and through linkage with the National Death Index. Outcomes evaluated were death from IHD (ICD-10 codes I20-I25) and overall mortality (deaths from all causes).

On the baseline questionnaire, participants current, past, or never use of menopausal estrogen and progestin, information on Premarin™ dose, ages at and years of use. Similar information was collected for other estrogens. This analysis restricts ET to pill or patch use. We collected similar information on progestin use. A later follow-up questionnaire updated information about current use of HT beginning in May 2000.

Statistical analysis

Characteristics of women were compared by age group and by HT status using t-tests for continuous variables and Pearson chi-square statistics for categorical variables. Multivariable Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations between current or past HT use at baseline and all-cause mortality or death from IHD. Age in days was used to define the time scale [16,17], with an additional adjustment for age at baseline (categorized as ≤59, 60–64, 65–69, 70–74, 75–84, or 85–94 years). Left truncation of survival times was dealt with by setting up appropriate age at cohort entry and at exit variables for use in PROC PHREG in SAS (version 9.2, Cary, NC). Follow-up began from the date that the baseline questionnaire was returned until either December 31, 2004 or a women's date of death, whichever was first. In this analysis HT status (current user, former user, etc.) at baseline was used as a time-independent covariate in the Cox regression. We also performed a time-dependent analysis using data from the later questionnaire. For the time-dependent analysis if a current user at baseline no longer reported use of hormones on follow-up then she was treated as a former user in risk sets indexed by deaths occurring later than the date she returned the follow-up questionnaire. In earlier risk sets she was treated as a current user. Women who did not return the later questionnaire were censored on May 1, 2000 in the time-dependent analysis. Otherwise follow-up was terminated on December 31, 2004.

Models were stratified by race/ethnicity and included the following potential confounders:

BMI (kg/m^2; 16–<18, 18–<22.5, 22.5–<25, 25–<30, 30 –≤54.9, or missing/invalid (i.e. <16 kg/m^2 or >54.9 kg/m^2), smoking status (never, past, current), pack-years of smoking (continuous), alcohol consumption (>20g/d, < 20 g/d and past drinkers), recent recreational

physical activity (hours/week), total caloric intake, calories from fat, protein, and cholesterol during the year before baseline, self-reported history of diabetes, high blood pressure, myocardial infarction or heart disease, cancer other than non-melanoma skin cancer, and stroke (yes/no).

By adding additional terms to the models described above, we estimated effects for type of HT used, duration of use, age at first use, and years from menopause to first use, using likelihood ratio tests. Type of therapy had five categories: ET, EPT, mixed use of ET and EPT and other/unknown including uncategorized hormone use and women reporting no hormone use. In our main statistical analysis we combined women reporting current use of either ET or EPT into a current HT users category, and we did a similar categorization for past use. In additional analyses we assessed whether differential effects of HT type (ET only or EPT) were evident.

We included interaction terms to investigate whether age at first use of HT was a modifier of the effects of current or past HT use. We also included interaction terms for age at baseline and current or past HT use to investigate whether age at baseline modified the effect of HT on all-cause mortality and on IHD mortality. The mean age for each age at baseline category was used in the models to test for trend and for linear interactions with HT use.

We used Wald tests to assess the age × HT interactions (specifically, to test the interaction between age at first HT use and current or past HT use). We considered two-sided p-values less than 0.05 as statistically significant. All analyses were conducted using SAS (version 9.2, Cary, NC)

Results

Baseline characteristics

As expected the frequency of deaths from all causes and deaths due to IHD over the follow-up period (ranging from 5–7 years) rose markedly with increasing age at baseline (Table 1).

Current HT users were less likely to have a BMI of 30 kg/m^2 or greater, to be current smokers, and more likely to engage in physical activity, be current alcohol drinkers and consume more calories than never or former HT users (Table 2). Current HT users were less likely to report a history of heart disease, and reported a lower baseline prevalence of cancer, stroke, and diabetes than former or never HT users. As can be seen in Table 1 however, current HT users were also younger than former or never HT users so that the crude differences shown in Table 2 cannot be interpreted easily without additional age correction such as that provided by Cox regression for the comparisons of mortality outcomes between HT groups.

Hormone use in later follow-up

Of the 37,912 women reporting current HT use at baseline 24,911 (66%) returned the follow-up questionnaire and provided data on HT use. Of these women, 5,144 (21%) reported no current use of ET or EPT at that time. Of the 33,325 women not reporting current use of HT at baseline 21,847 (66%) returned the later questionnaire. Continued use of HT was related to age at baseline with 81 percent of current users at baseline aged less than 65 years reporting continued use at follow-up compared to 69 percent of current users at baseline aged 75 or older.

Mortality during follow-up by HT use

During follow-up, deaths were reported in 18.3% of never users of HT and 17.9% of former users, compared to 6.9% of women currently taking HT at baseline. Fewer deaths from IHD occurred among current HT users (1.0%) than among never (3.7%) users or former (3.0%) users. The Cox model (above) compared age-specific hazards of mortality by HT status. We found that hormone therapy use at baseline was associated with an overall reduction in risk of all-cause and IHD mortality (Tables 3 and 4). Women who currently took HT had a hazard of death from all causes that was 0.83 times that of never users (95% CI=0.79–0.87), and their hazard of death from IHD was 0.84 times that of never users (95% CI=0.74–0.95). Mortality risk was also lower among former HT users than never users (all-cause mortality HR=0.88, 95% CI=0.83–0.93; IHD mortality HR=0.81, 95% CI=0.71–0.92).

Effects of HT by age

Age at baseline was a strong modifier of the relationship between current use at baseline of HT and all-cause mortality. For women using HT at baseline, the hazard ratios increased with increasing age category for all-cause mortality ($p_{trend}<0.0001$) suggesting that the reduction in relative risk associated with current HT use diminishes as age increases (Table 3). For women 75 years or older, using hormones at baseline, the risk of death was not significantly reduced (age 75–84 years: HR=1.00, 95% CI = 0.91–1.09; age 85–94 years: HR=0.94, 95% CI = 0.81–1.10). In contrast to the pattern seen for current use, former use, while significantly protective overall, showed no marked variation in risk of all-cause mortality by age.

For IHD mortality, a similar risk pattern was observed where the marked reduction in risk associated with HT use at baseline declined with increasing age at baseline ($p_{trend}=0.008$; Table 4). The protective effect of current use was very striking for women aged ≤59 years (HR=0.38, 95% CI=0.22–0.67) but virtually vanished by age 75–84 (HR=0.93, 95% CI=0.77–1.12). As with overall mortality, former HT use showed no trend in risk of IHD mortality by age ($p_{trend}=0.24$).

Additional analyses

Other aspects of HT use that may affect all-cause mortality or IHD mortality, such as formulation (ET vs. EPT), duration, age at first use, and years since menopause at first use, were assessed (Table 5 and Table 6). None of these factors appeared influential (all confidence limits overlapped 1) when added to a model that included status of HT use at baseline and the interaction of this status with age at baseline. Treating HT use as a time-dependent variable, as described in the statistical methods, gave results that were both qualitatively and quantitatively extremely similar to those in Tables 3 and 4.

Conclusion

The risk for all-cause mortality was decreased by 45% or more among women under age 65 years who reported currently taking HT at baseline, compared to similarly aged women who reported no history of HT use. On the other hand, women aged 75 years or older at baseline who reported currently taking HT were at similar risk of death as never users. The statistical significance of this inverse trend with age in the protective effect of HT was very strong reflecting both the strength of this trend and the large number of HT users participating in our study. Other variables, such as duration of HT use, or age at start of use were far less significant modifiers of the HT effects than was current age.

For death caused by IHD, we observed the same pattern as for all-cause mortality, with HRs attenuating toward the null with increasing age ($p_{trend}=0.008$). Thus, even though the overall

risk of IHD mortality was reduced overall by HT, the protective effect weakened considerably with use at older ages.

Discussion

Our results showing an overall reduction in risk of all-cause and IHD mortality with HT use are consistent with those from previous observational studies, but not with those from clinical trials. However, our results for all-cause mortality with HT use by age group were generally comparable to those from the WHI trial [10] which found decreased risk in women randomized at age 50–59 (RR=0.70; 95% CI 0.51–0.96) and increased risk in women randomized at age 70–79 (RR=1.14; 95% CI 0.94–1.37). That is, age appears to modify the relationship between HT and mortality both in our study and in the WHI randomized trial, with both studies showing a similar trend of HRs increasing with increasing age. It has been argued that increased risk of CHD among HT users in the WHI clinical trial is likely related to the age (or time duration since menopause) at first use of HT[11,12]. Another explanation is that it is a woman's current age rather than her age at first use that modifies the effect of HT. Due to the relatively short follow-up period and more confined age range for the WHI trial, that study could not differentiate age at randomization from age at current use. In contrast, we were able to estimate the influence of these two age periods separately as modifying variables. Assuming that self-reported baseline HT use reflected a women's usage pattern over the follow-up period; (and our data from 2000–2001 indicate that the majority (79 percent) of current users of HT at baseline remained current users at that time), our results suggest that it is age at current use that is the important determinant. We found that age at baseline was a more significant modifier of the relationship between HT use at baseline and both all-cause mortality and IHD mortality than was age at, or years since menopause and first use. We interpret this finding as evidence that current age, rather than age at first use, is relevant to the reduced hazards of all-cause and IHD mortality. Therefore, the implications of our findings are similar for older women who are current HT users of long duration, as well as for older women who might be currently considering whether to begin using HT for the first time.

Several potential biases, including selection bias, compliance bias, follow-up bias, and inadequate control of confounding may account for the protective effects of HT use on mortality that have been seen in observational studies. Our study may be subject to the previously described "healthy woman effect," whereby women taking HT have more education and are of higher social class, and are more compliant, healthier, and with a more favorable lifestyle than nonusers [1]. Education and social class are strongly inversely associated with risk factors for CHD [18]. However, since participants in our study were all public school teachers or administrators in California, our sample is homogeneous in some characteristics; and more uniform with respect to education and socioeconomic status than some other cohorts. It may be, therefore, less likely that education or social class were confounders of the relationship between HT use and risk of death from IHD in our study. The follow-up period for the current analysis includes a span of approximately 2.5 years subsequent to the widely publicized WHI results [9] (mid-2002 to the end of 2004). Based on other studies showing a profound impact of the WHI results on HT use in the general population [19–21], many CTS participants who reported current HT use at baseline would have ceased using HT by the end of the follow-up period. It seems unlikely however that cessation of hormone use or any of the aforementioned biases caused the modifying effect of age at baseline observed in this cohort.

An additional concern is that we may have missed short term increases in the risk of mortality occurring shortly after the beginning of HT therapy, due to left truncation of women who die or are otherwise less likely to participate shortly after a disease event.

Hernan et al [13] found increased risk of CHD incidence in the two years after start of HT therapy in the data from the Nurses' Health Study, by examining a series of nested "non-randomized trials" of CHD disease incidence in HT initiators and non-initiators, over a total of 8 contact/recontact cycles, while using time of HT initiation rather than time of questionnaire as the start of observation in these "trials". We are not able to replicate these analyses since we do not obtain CHD incidence for the teachers, and are reliant upon mortality data. While missing such short term events could have led to biased estimates of the overall effect of HT on mortality ('initiation bias'), we find it unlikely that this would have lead to the distinct age × HT interactions that are seen so strongly here. Nor would this issue appear to negate the implications of our findings for older women who started HT close to close to menopause about whether or not they now benefit from continued HT use. Our study of the relative importance of the two time-related variables, age at start of HT vs. age at baseline, implies that they do not.

A strength of this analysis is the high proportion of CTS participants, even those at a relatively advanced age, who reported current HT use on the baseline questionnaire. This provided considerable statistical power to estimate the effects of use over a wide age range. Furthermore, the broad age distribution of women in the CTS and the wide diversity in ages at first HT use allowed us to address questions about the modifying effects of current age, as distinct from the modifying effect of age at first use. In summary, our study suggests that the health consequences of HT vary primarily by age of current use, with age at first use being of negligible independent importance. We found an association between current use at baseline and reduced risk for all-cause mortality in younger, but not older, postmenopausal women in the CTS. Our results add to the growing evidence that hormone use may have beneficial effect in younger women, but have little cardiovascular benefit in older women, and has direct implications regarding the lack of potential benefits of continued use of HT therapy for older women who began HT close to menopause.

Acknowledgments

We thank the current and retired California teachers and administrators who are participants in the CTS for their long-term support of this study. We would also like to thank the CTS Steering Committee who are responsible for the formation and maintenance of the cohort but who did not participate in the present analysis and paper: Hoda Anton-Culver, Christina A. Clarke, Rosemary Cress, Dennis Deapen, Joan Largent, Rich Pinder, Dee W. West, and Argyrios Ziogas.

This study was supported by the by grant R01 CA77398 from the National Institutes of Health and by the California Breast Cancer Act of 1993, California Department of Health Services. The collection of cancer incidence data used to define one of the variables in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35139 awarded to the University of Southern California, contract N01-PC-35136 awarded to the Northern California Cancer Center, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. Additional support for work by Daniel Stram and Giske Ursin was provided by the NCI grant number P01 CA 017054-30. The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

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Table 1

Selected Baseline Characteristics in Relation to Age Groups in 71,237 Women Eligible for the Analysis of All-Cause Mortality

	Age Group					
	36–59* n=30080	**60–64* n=10816**	**65–69* n=10438**	**70–74* n=8143**	**75–84* n=9604**	**85–94* n=2156**
			Risk Factors			
BMI†						
<18	337 (1.1)	120 (1.1)	114 (1.1)	114 (1.4)	175 (1.8)	79 (3.7)
18–22.5	9844 (32.7)	2925 (27.0)	2783 (26.7)	2135 (26.2)	2608 (27.2)	699 (32.4)
22.5–25	6771 (22.5)	2473 (22.9)	2404 (23.0)	1922 (23.6)	2202 (22.9)	430 (19.9)
25–30	7575 (25.2)	3108 (28.7)	3038 (29.1)	2305 (28.3)	2479 (25.8)	372 (17.3)
>30	4769 (15.9)	1732 (16.0)	1507 (14.4)	993 (12.2)	879 (9.2)	95 (4.4)
Unknown	784 (2.6)	458 (4.2)	592 (5.7)	674 (8.3)	1261 (13.1)	481 (22.3)
Smoking						
Never	17893 (59.5)	5963 (55.1)	5819 (55.8)	4866 (59.8)	6130 (63.8)	1574 (73.0)
Former	10214 (4.0)	4109 (38.0)	3922 (37.6)	2802 (34.4)	3052 (31.8)	534 (24.8)
Current	1973 (6.6)	744 (6.9)	697 (6.7)	475 (5.8)	422 (4.4)	48 (2.2)
Alcohol						
Never	4745 (15.8)	1839 (17.0)	1999 (19.2)	1757 (21.6)	2379 (24.8)	668 (31.0)
Former	4250 (14.1)	1361 (12.6)	1381 (13.2)	1053 (12.9)	1405 (14.6)	346 (16.1)
Current, <20 g/d	17476 (58.1)	5941 (54.9)	5441 (52.13)	4103 (50.4)	4206 (43.8)	746 (34.6)
Current, ≥20 g/d	2687 (8.9)	1288 (11.9)	1150 (11.0)	744 (9.1)	683 (7.1)	95 (4.4)
Unknown	922 (3.1)	387 (3.6)	467 (4.5)	486 (6.0)	931 (9.7)	301 (14.0)
			Hormone Use and Mortality			
Hormone therapy						
Never	5525 (18.4)	2429 (22.5)	2999 (28.7)	2422 (29.7)	3347 (34.9)	1152 (53.4)
Former	2658 (8.8)	1510 (14.0)	1859 (17.8)	1987 (24.4)	2845 (29.6)	567 (26.3)
Current	20111 (66.9)	6351 (58.7)	5030 (48.2)	3257 (40.0)	2848 (29.7)	315 (14.6)
Other	1786 (5.9)	526 (4.9)	550(5.3)	477 (5.9)	564 (5.9)	122 (5.7)
Death						
No	29227 (97.2)	10196 (94.3)	9435 (90.4)	6871 (84.4)	6424 (66.9)	685 (31.8)
Yes	853(2.8)	620 (5.7)	1003(9.6)	1272 (15.6)	3180(33.1)	1471(68.2)

	Age Group					
	36–59* n=30080	**60–64* n=10816**	**65–69* n=10438**	**70–74* n=8143**	**75–84* n=9604**	**85–94* n=2156**
IHD death						
No	30017 (99.8)	10756 (99.5)	10325 (99.0)	7953 (97.7)	8950 (93.2)	1754 (81.4)
Yes	55 (0.2)	54 (0.5)	110 (1.1)	189 (2.3)	654 (6.8)	402(18.7)

	Age Group					
	36–59* n=30174	**60–64* n=10816**	**65–69* n=10438**	**70–74* n=8143**	**75–84* n=9604**	**85–94* n=2156**
Medical History						
Prior heart attack						
No	29839 (99.2)	10632 (98.3)	10139 (97.1)	7806 (95.9)	8993 (93.6)	1946 (90.3)
Yes	156 (0.5)	147 (1.4)	266 (2.6)	293 (3.6)	542 (5.6)	169 (7.8)
Unknown	85 (0.3)	37 (0.3)	33 (0.3)	44 (0.5)	69 (0.7)	41 (1.9)
Prior stroke						
No	29752 (98.9)	10643 (98.4)	10239 (98.1)	7884 (96.8)	9102 (94.8)	1975 (91.6)
Yes	243 (0.8)	136 (1.3)	166 (1.6)	215 (2.6)	433 (4.5)	140 (6.5)
Unknown	85 (0.3)	37 (0.3)	33 (0.3)	44 (0.5)	69 (0.7)	41 (1.9)
Prior cancer						
No	26883 (89.4)	9318 (86.2)	8682 (83.2)	6479 (79.6)	7212 (75.1)	1567 (72.7)
Yes	3197 (10.6)	1498 (13.9)	1756 (16.8)	1664 (20.4)	2392 (24.9)	589 (27.3)
Prior diabetes						
No	29243 (97.2)	10342 (95.6)	9909 (94.9)	7658 (94.0)	9016 (93.9)	2012 (93.3)
Yes	752 (2.5)	437 (4.0)	496 (4.8)	441 (5.4)	519 (5.4)	103 (4.8)
Unknown	85 (0.3)	37 (0.3)	33 (0.3)	44 (0.5)	69 (0.7)	41 (1.9)
Behavioral Factors**						
Physical activity‡, hrs/wk/yr	3.5 ± 3.9	4.0 ± 4.4	4.2 ± 4.4	3.9 ± 4.4	3.0 ± 4.0	1.6 ± 3.0
Dietary calories, kcal	1603.4 ± 554.3	1473.8 ± 500.3	1458.4 ± 475.2	1434.9 ± 470.3	1426.4 ± 484.9	1441.9 ± 518.7
Dietary calories from fat, kcal/d	508.9 ± 243.8	464.6 ± 222.9	456.0 ± 214.4	449.2 ± 214.9	452.8 ± 217.2	485.4 ± 230.4
Dietary calories from protein, kcal/d	251.1 ± 95.5	233.1 ± 89.3	234.6 ± 87.7	232.6 ± 87.8	231.5 ± 90.9	232.1 ± 94.8
Daily dietary cholesterol, mg	194.3 ± 108.2	184.6 ± 106.0	184.0 ± 107.4	181.5 ± 106.4	184.1± 109.1	200.7 ± 123.4

*Data presented as No. (%) for categorical variables, or mean ± SD for continuous variables.

† BMI: body mass index, calculated as weight in kilograms divided by height in meters squared.

‡ Physical activity: combination of strenuous and moderate activities in past three years.

Note: All comparisons across age groups were significant ($p<0.0001$).

** Computed on subjects with known values.

Table 2

Selected Baseline Characteristics in Relation to Hormone Therapy in 71,237 Women Eligible for the Analysis of All-Cause Mortality

	Hormone Therapy				
	Never* n=17874	Former* n=11426		Current* n=37912	
	Freq. (%)	Freq. (%)	p-value[a]	Freq. (%)	p-value[a]
	Risk Factors				
BMI[†]					
<18	294 (1.6)	162 (1.4)		426 (1.1)	
18–22.5	4648 (26.0)	3029 (26.5)		12121 (32.0)	
22.5–25	3747 (21.0)	2521 (22.0)	<.0001	9054 (23.9)	<.0001
25–30	4708 (26.3)	3203 (28.0)		9916 (26.2)	
>30	2940 (16.5)	1659 (14.5)		4819 (12.7)	
Other/Unknown	1537 (8.6)	852 (7.5)		1576 (4.2)	
Smoking					
Never	11088 (62.0)	6660 (58.3)	<.0001	22054 (58.2)	<.0001
Former	5463 (30.6)	4074 (35.7)		13731 (36.2)	
Current	1323 (7.4)	692 (6.1)		2127 (5.6)	
Alcohol					
Never	4222 (23.6)	2335 (20.4)		6082 (16.0)	
Former	2655 (14.9)	1687 (14.8)	<.0001	4854 (12.8)	<.0001
Current, <20 g/d	8446 (47.3)	5650 (49.5)		21710 (57.3)	
Current, ≥20 g/d	1499 (8.4)	1064 (9.3)		3745(9.9)	
Unknown	1052 (5.9)	690 (6.0)		1516 (4.0)	
	Medical History				
Prior heart attack					
No	17252 (96.5)	10991 (96.2)	0.0003	37194 (98.1)	<.0001
Yes	504 (2.8)	389 (3.4)		590 (1.6)	
Unknown	118 (0.7)	46 (0.4)		128 (0.3)	
Prior stroke					
No	17343 (97.0)	11066 (96.8)	0.001	37271 (98.3)	<.0001

	Hormone Therapy				
	Never* n=17874	Former* n=11426		Current* n=37912	
	Freq. (%)	Freq. (%)	p-value[a]	Freq. (%)	p-value[a]
Yes	413 (2.3)	314 (2.8)		513 (1.4)	
Unknown	118 (0.7)	46 (0.4)		128 (0.3)	
Prior cancer					
No	14184 (79.4)	8027 (70.3)	<.0001	34533 (91.1)	<.0001
Yes	3690 (20.6)	3399 (29.7)		3379 (8.9)	
Prior diabetes					
No	16793 (94.0)	10842 (94.9)	0.0005	36708 (96.8)	<.0001
Yes	963 (5.4)	538 (4.7)		1076 (2.8)	
Unknown	118 (0.7)	46 (0.4)		128 (0.3)	
		Mortality			
Death					
No	14606 (81.7)	9376 (82.1)	0.46	35292 (93.1)	<.0001
Yes	3268 (18.3)	2050 (17.9)		2620 (6.9)	
Death from IHD					
No	17219 (96.4)	11076 (97.0)	0.005	37508 (99.0)	<.0001
Yes	653 (3.7)	347 (3.0)		391 (1.0)	

	Hormone Therapy				
	Never*	Former*		Current*	
		Mean ± SD	p-value[a]	Mean ± SD	p-value[a]
	Behavioral Factors**				
Physical Activity‡, hrs/wk/yr	3.5 ± 4.3	3.4 ± 4.1	0.33	3.7 ± 4.1	<.0001
Daily dietary calories, kcal	1498.5 ± 535.5	1484.4 ± 508.8	0.03	1534.3 ± 518.7	<.0001
Dietary calories from fat, kcal/d	480.4 ± 237.2	466.6 ± 226.1	<.0001	483.2 ± 229.8	0.21
Dietary calories from protein, kcal/d	239.1 ± 95.2	237.2 ± 91.7	0.11	242.7 ± 91.2	<.0001
Dietary cholesterol, mg/d	191.1 ± 114.1	186.9 ± 110.9	0.003	188.1 ± 104.8	0.005

* Data presented as No. (%) for categorical variables, or mean ± SD for continuous variables.

[a] p-value: compare former user vs. non-users and current uses vs. non-users, calculated using chi-square for categorical variables, t-test for continuous variables.

[†] BMI: body mass index, calculated as weight in kilograms divided by height in meters squared.

[‡] Physical activity: combination of strenuous and moderate activities in past three years

[**] Computed on subjects with known values.

Table 3

Multivariate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the Association between Hormone Therapy and Overall Mortality by Age at Questionnaire

	Hormone Therapy							
	Never		Former			Current		
	No. of deaths	No. of person years	No. of deaths	No. of person years	HR (95% CI)*	No. of deaths	No. of person years	HR (95% CI)*
Overall†	3268	147074	2050	94292	0.88 (0.83–0.93)	2620	329482	0.83 (0.79–0.87)
Age Group								
36–59	259	48237	121	23197	0.95 (0.77–1.17)	425	178234	0.54 (0.46–0.62)
60–64	198	20983	109	13051	0.91 (0.72–1.14)	282	55783	0.65 (0.54–0.77)
65–69	344	25551	210	15831	0.99 (0.84–1.17)	403	43531	0.82 (0.71–0.94)
70–74	430	20176	327	16562	0.86 (0.75–0.98)	440	27576	0.84 (0.74–0.96)
75–84	1223	25262	906	22144	0.87 (0.80–0.94)	868	22388	1.00 (0.91–1.09)
85–94	814	6865	377	3505	0.89 (0.79–1.00)	202	1970	0.94 (0.81–1.10)
P for trend‡					0.39			<.0001

*Cox regression models included age at questionnaire, status of hormone therapy and their interaction, stratified by race, adjusted for BMI, smoking, total pack-years, alcohol consumption, physical activity during past three years, dietary intake, other hormone, and prior history of heart attack, stroke, cancer, and diabetes.

†Overall estimates using models mentioned above without interaction between age and hormone therapy.

‡Test for trend (interaction) using mean age of each group as continuous variable. Cox regression models stratified by race, and adjusted for all potential confounders.

Table 4

Multivariate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the Association between Hormone Therapy and IHD Death by Age at Questionnaire

	Hormone Therapy							
	Never		Former			Current		
	No. of IHD deaths	No. of person years	No. of IHD deaths	No. of person years	HR (95% CI)	No. of IHD deaths	No. of person years	HR (95% CI)
Overall[†]	653	147055	347	94265	0.81 (0.71–0.92)	391	329370	0.84 (0.74–0.95)
Age Group								
36–59	23	48219	4	23189	0.37 (0.13–1.06)	26	178190	0.38 (0.22–0.67)
60–64	19	20983	6	13042	0.52 (0.21–1.27)	24	55742	0.53 (0.30–0.93)
65–69	42	25551	21	15831	0.92 (0.55–1.54)	44	43504	0.76 (0.50–1.16)
70–74	63	20176	48	16554	0.92 (0.64–1.32)	69	27576	0.90 (0.65–1.26)
75–84	270	25262	168	22144	0.78 (0.64–0.94)	178	22388	0.93 (0.77–1.12)
85–94	236	6865	100	3505	0.87 (0.69–1.11)	50	1970	0.86 (0.63–1.17)
P for trend[‡]					0.24			0.008

[*] Cox regression models included age at questionnaire, status of hormone therapy and their interaction, stratified by race, adjusted for BMI, smoking, total pack-years, alcohol consumption, physical activity during past three years, dietary intake, other hormone, and prior history of heart attack, stroke, cancer, and diabetes.

[†] Overall estimates using models mentioned above without interaction between age and hormone therapy.

[‡] Test for trend (interaction) using mean age of each group as continuous variable. Cox regression models stratified by race and adjusted for all potential confounders.

Table 5

Effects of Different Types of Hormone, Duration of Hormone Use, Age Starts Hormone Therapy, and Years from menopause to HT use in Relation to Overall Mortality

	Frequency (%)	No. of death	No. of person years	Remaining effect HR (95% CI)*	p-value†
Types of hormone					0.48
E only	21868 (30.70)	3347	183097	1 (ref)	
E+P only	21624 (30.36)	945	189719	0.97 (0.89–1.05)	
E and E+P	8578 (12.04)	748	74003	0.96 (0.88–1.04)	
Other/Unknown**	19167 (26.91)	3359	158225	1.19 (1.07–1.33)	
Duration of hormone use					0.50
≤4 yrs	21623 (30.35)	1603	187298	1 (ref)	
4–7.5 yrs	7294 (10.24)	508	63412	1.00 (0.90–1.11)	
7.5–17 yrs	11235 (15.77)	924	97050	0.98 (0.90–1.07)	
>17 yrs	7009 (9.84)	1246	58157	1.05 (0.96–1.15)	
Other/Unknown**	24076 (33.80)	4118	199128	1.25 (1.12–1.38)	
Age starts hormone therapy					0.50
<45	10487 (14.72)	993	90136	1 (ref)	
45–54	29388 (41.25)	2408	253690	0.96 (0.89–1.04)	
55–64	8275 (11.62)	941	70590	0.97 (0.88–1.06)	
≥65	1820 (2.55)	381	14841	0.91 (0.81–1.03)	
Other/Unknown**	21267 (29.85)	3676	175787	1.33 (1.09–1.62)	
Years from menopause to hormone therapy					0.54
0	11165 (15.67)	913	96392	1 (ref)	
1–5	15733 (22.09)	1278	135853	1.05 (0.97–1.15)	
5–10	5335 (7.49)	526	45792	1.07 (0.96–1.20)	
>10	3157 (4.43)	536	26258	1.05 (0.94–1.18)	
Other/Unknown**	35847 (50.32)	5146	300750	1.06 (0.99–1.14)	

Abbreviations: E, estrogen; P, progestin; HR, hazard ratio; CI, confidence interval.

*Hazard ratios for types of hormone, duration of hormone use, age starts hormone therapy, and years from menopause to hormone therapy respectively, when these variables are added to Cox regression models containing terms for age at questionnaire, hormone therapy status, and interactions between age and current and former hormone use. Models were adjusted for BMI, smoking, total pack-years, alcohol consumption, physical activity during past three years, dietary intake, and prior history of heart attack, stroke, cancer, and diabetes, and stratified by race.

† p-value for Wald tests when not considering the Other/Unknown category.

** Other/Unknown category includes never users of HT.

Table 6

Effects of Different Types of Hormone, Duration of Hormone Use, Age Starts Hormone Therapy, and Years from menopause to HT use in Relation to IHD Death

	Frequency (%)	No. of death	No. of person years	Remaining effect HR (95% CI)*	p-value†
Types of hormone					0.22
E only	21865 (30.70)	605	183073	1 (ref)	
E+P only	21614 (30.35)	91	189629	0.84 (0.66–1.07)	
E and E+P	8575 (12.04)	103	73978	0.87 (0.70–1.08)	
Other/Unknown**	19165 (26.91)	665	158207	1.34 (1.02–1.75)	
Duration of hormone use					0.22
≤4 yrs	21618 (30.35)	250	187253	1 (ref)	
4–7.5 yrs	7293 (10.24)	59	63403	0.79 (0.59–1.06)	
7.5–17 yrs	11228 (15.77)	128	96990	0.92 (0.73–1.15)	
>17 yrs	7007 (9.84)	231	58139	1.06 (0.85–1.32)	
Other/Unknown**	24073 (33.80)	796	199102	1.18 (0.92–1.53)	
Age starts hormone therapy					0.58
<45	10483 (14.72)	147	90100	1 (ref)	
45–54	29379 (41.25)	380	253615	1.05 (0.87–1.27)	
55–64	8272 (11.61)	137	70563	0.91 (0.72–1.15)	
≥65	1820 (2.56)	77	14841	0.99 (0.75–1.31)	
Other/Unknown**	21265 (29.86)	723	175768	1.83 (1.13–2.98)	
Years from menopause to hormone therapy					0.83
0	11161 (15.67)	137	96357	1 (ref)	
1–5	15727 (22.08)	196	135799	1.06 (0.85–1.32)	
5–10	5335 (7.49)	87	45792	1.11 (0.85–1.46)	
>10	3157 (4.43)	94	26258	0.99 (0.76–1.30)	
Other/Unknown**	35839 (50.34)	950	300682	0.99 (0.82–1.19)	

Abbreviations: E, estrogen; P, progestin; HR, hazard ratio; CI, confidence interval.

*Hazard ratios for types of hormone, duration of hormone use, age starts hormone therapy, and years from menopause to hormone therapy respectively, when these variables are added to Cox regression models containing terms for age at questionnaire, hormone therapy status, and interactions between age and current and former hormone use. Models were adjusted for BMI, smoking, total pack-years, alcohol consumption, physical activity during past three years, dietary intake, and prior history of heart attack, stroke, cancer, and diabetes, and stratified by race.

† p-value for Wald tests when not considering the Other/Unknown category.

** Other/Unknown category includes never users of HT.