Hormone replacement therapy and the risk of subarachnoid hemorrhage in postmenopausal women

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OBJECTIVE The incidence of subarachnoid hemorrhage (SAH) increases after menopause. Anecdotal data suggest that hormone replacement therapy (HRT) may reduce the rate of SAH and aneurysm formation in women. The goal of this study was to determine the effect of HRT on occurrence of SAH in a large prospective cohort of postmenopausal women.

METHODS The data were analyzed for 93,676 women 50–79 years of age who were enrolled in the observational arm of the Women's Health Initiative Study. The effect of HRT on risk of SAH was determined over a period of 12 ± 1 years (mean $\pm$ SD) using Cox proportional hazards analysis after adjusting for potential confounders. Additional analysis was performed to identify the risk associated with "estrogen only" and "estrogen and progesterone" HRT among women.

RESULTS Of the 93,676 participants, 114 (0.1%) developed SAH during the follow-up period. The rate of SAH was higher among women on active HRT compared with those without HRT used (0.14% vs 0.11%, absolute difference 0.03%, $p < 0.0001$). In unadjusted analysis, participants who reported active use of HRT were 60% more likely to suffer an SAH (RR 1.6, 95% CI 1.1–2.3). Compared with women without HRT use, the risk of SAH continued to be higher among women reporting active use of HRT (RR 1.5, 95% CI 1.0–2.2) after adjusting for age, systolic blood pressure, cigarette smoking, alcohol consumption, body mass index, race/ethnicity, diabetes, and cardiovascular disease. The risk of SAH was nonsignificantly higher among women on "estrogen only" HRT (RR 1.4, 95% CI 0.91–2.0) than "estrogen and progesterone" HRT (RR 1.2, 95% CI 0.8–2.1) after adjusting for the above-mentioned confounders.

CONCLUSIONS Postmenopausal women, particularly those at risk for SAH due to presence of unruptured aneurysms, family history, or cardiovascular risk factors, should be counseled against use of HRT.

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KEY WORDS hormone replacement therapy; subarachnoid hemorrhage; postmenopausal women; estrogen replacement; vascular disorders; intracranial aneurysm

THE risk of intracranial aneurysm formation and subarachnoid hemorrhage (SAH) is higher in postmenopausal women compared with premenopausal women.^{8,13,18,19,28} Reduced levels of estrogen in postmenopausal women may increase the risk of aneurysm formation and rupture by reduction in collagen and elastin content and reduced elasticity of arterial walls.³ In an experimental intracranial aneurysm mouse model, estrogen prevented aneurysmal rupture in ovariectomized mice.³⁰ The protective effect of estrogen seemed to occur through activation of estrogen receptor- β , a predominant subtype of estrogen receptor in human intracranial aneurysms and cerebral arteries. Hormone replacement therapy (HRT)

was associated with reduced risk of spontaneous SAH in postmenopausal women in most^{19,22} but not all case control studies.²⁵ The Women's Health Initiative (WHI) randomized trial³³ assessed the effect of estrogen plus progestin on ischemic and hemorrhagic stroke in 608 women 50–79 years of age with an average follow-up of 5.6 years. There was a nonsignificant protective effect on hemorrhagic stroke (HR 0.82, 95% CI 0.43–1.56). However, the study was underpowered because there were only 10 SAH events among the randomized patients. A meta-analysis²⁴ found a small nonsignificant protective effect of HRT on risk of SAH (HR 0.8, 95% CI 0.57–1.04).

We performed this study to determine the effect of

ABBREVIATIONS HRT = hormone replacement therapy; RR = relative risk; SAH = subarachnoid hemorrhage; SE = standard error; WHI = Women's Health Initiative.

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HRT on risk of SAH in a large prospective cohort of postmenopausal women.

Methods

We analyzed the data for 93,676 women 50–79 years of age who were enrolled in the observational arm of the WHI study.^{2,15} Briefly, women who were screened for the clinical trial but proved to be ineligible or unwilling to be randomized were offered the opportunity to enroll in the observational arm. Study participants were enrolled at 40 centers throughout the US between October 1, 1993, and December 31, 1998. Potential subjects were excluded if they did not plan to reside in the area for at least 3 years, had medical conditions predictive of survival less than 3 years, or had complicating conditions such as alcoholism, drug dependency, or dementia. All participants provided informed consent using materials approved by Institutional Review Boards at each center. Demographic and risk exposure data, as well as data regarding family and medical history, were obtained by self-report using standardized questionnaires at baseline assessment. Certified staff took physical measurements, including blood pressure, height and weight, and blood samples at the clinic visit.³⁴ For postmenopausal hormone treatment, detailed information was obtained on the preparation, estrogen and progesterone dose, schedule, and route of administration.

Recruitment for the observational study was completed in 1998 and participants were followed for 8–12 years. Annual, mailed follow-up forms updated information on HRT and other selected risk factor information and structured initial reporting of clinical events.⁷ Specific details of illnesses and stroke hospitalizations were obtained as needed via a standardized questionnaire administered by phone, in-person interview, or self-completed form. Portions of the medical record (discharge summary and results of relevant diagnostic and laboratory tests) were requested, assembled, and provided to the designated local adjudicator, who adjudicated the event. A fraction of the stroke events in the observational study were reviewed by central neurologists for quality control.⁷ In a previous analysis of the WHI clinical trial, 94.5% of stroke events identified by the local adjudicator were confirmed on central review, while 93.8% of centrally adjudicated strokes had been classified as strokes by local adjudicators.³³ Following notice of a participant's death, information was obtained on any outcomes occurring between the participant's last routine contact and her date of death. To ascertain survival and cause of death for all WHI participants, data linkage with the National Death Index of the National Center for Health Statistics was used. WHI participants who are lost to follow-up or who are known to be dead were matched to the National Death Index to search for otherwise unreported deaths and to ascertain causes of death.

Statistical Analysis

Because the interval of follow-up varied among study participants, Cox proportional hazards analysis was used to estimate the relative risk (RR) for SAH using IBM SPSS statistical software (IBM Corp.). We evaluated the RR for any HRT use (previous or active at time of baseline

assessment), active use at baseline assessment, and type of replacement therapy ("estrogen only" vs "estrogen and progesterone"). The potential confounders were identified from previous reports^{1,3} and from univariate analysis of demographic and clinical variables between women who did or did not develop SAH. We used chi-square and ANOVA for categorical and continuous variables, respectively. The multivariate adjusted Cox proportional hazards model adjusted for differences in age, sex, race/ethnicity (African American, white, others), systolic blood pressure (continuous variable), body mass index (cm/kg [continuous variable]), cigarette smoking (never, former, current), alcohol consumption (≥ 7 drinks per week, 1 to < 7 drinks per week, and other [nondrinker, past drinker, < 1 drink per month, or < 1 drink per week]), diabetes mellitus, and cardiovascular disease that were significantly different in univariate analysis. We calculated 95% CIs using a Taylor series approximation for the standard error (SE) of the RR. In another analysis, the adjusted RR of SAH was compared between participants who had never used HRT compared with those who had used HRT either in the past or were actively using HRT.

Results

Of 93,676 participants, a total of 114 (0.1%) developed SAH during the follow-up period of 12 ± 1 (mean $\pm$ SD) years. HRT was being used at baseline assessment by 41,630 of the 93,676 participants. The age at baseline assessment (mean $\pm$ SD) was significantly lower among participants who were actively using HRT compared with those who did not (62.0 ± 7.1 years vs 64.9 ± 7.3 years, $p < 0.0001$) (Table 1). The proportion of participants 70–79 years of age was lower among those who were actively using HRT (16.9% vs 30.2%, $p < 0.0001$). The body mass index (mean $\pm$ SD) was lower among participants who were actively using HRT (26.5 ± 5.2 vs 27.9 ± 6.0 , $p < 0.0001$). The initial systolic blood pressure (mean $\pm$ SD) was significantly lower among participants who were actively using HRT compared with those who did not (125.5 ± 17.5 versus 128.1 ± 18.3 , $p < 0.0001$). There was a higher proportion of participants with diabetes mellitus (5.6% vs 2.8%, $p < 0.0001$) and cardiovascular disease (19.8% vs 17.3%, $p < 0.0001$) among those who were not actively using HRT compared with those who were. There was a higher proportion of participants who were actively using HRT who admitted to having 7 or more drinks per week (12.9% vs 12.2%, $p = 0.007$). The proportion of participants who were either past or active cigarette smokers was higher among those who were actively using HRT (49.6% vs 47.3%, $p < 0.0001$). The proportion of patients with previous use of HRT was similar among those who were or were not actively using HRT (18.4% vs 14.9%, $p = 0.3$).

The proportion of participants who died during follow-up was significantly higher among those who developed SAH (44.2% vs 11.6%, $p < 0.0001$). The 10-year SAH-free survival was significantly lower among persons who reported active use of HRT (69.7%, 95% CI 69.6%–69.8%) or estrogen-only HRT (68.7%, 95% CI 68.6%–68.8%) compared with those who did not report active use of any replacement therapy (76.3%, 95% CI 76.2%–76.4%; Fig. 1).

TABLE 1. Baseline characteristics for postmenopausal women according to active use of HRT: WHI Observational Study*

Baseline Characteristics	No. of Participants (%)		p Value
	Women Actively Using HRT	Women Not Actively Using HRT	
Overall no. of participants	41,630	52,046	
Mean age in yrs	62.0 ± 7.1	64.9 ± 7.3	<0.0001
Age in yrs			<0.0001
50–54	7122 (17.1)	5260 (10.1)	
55–59	9317 (22.4)	8008 (15.4)	
60–69	18,152 (43.6)	23,044 (44.3)	
70–79	7039 (16.9)	15,734 (30.2)	
Body mass index, cm/kg (mean ± SD)	26.5 ± 5.2	27.9 ± 6.0	<0.0001
Body mass index categorical, cm/kg			<0.0001
Underweight (<18.5)	351 (0.8)	476 (0.9)	
Normal (18.5–24.9)	18,553 (44.6)	18,422 (35.4)	
Overweight (25.0–29.9)	13,929 (33.5)	17,563 (33.7)	
Obesity I (30.0–34.9)	5634 (13.5)	8982 (17.3)	
Obesity II (35.0–39.9)	1859 (4.5)	3594 (6.9)	
Extreme obesity III (≥40)	924 (2.2)	2376 (4.6)	
Race/ethnicity			<0.0001
White (not of Hispanic origin)	5479 (13.1)	2156 (4.1)	
African American	36,001 (86.5)	42,015 (80.7)	
Others	402 (1.0)	657 (1.3)	
Systolic blood pressure, mm Hg (mean ± SD)	125.5 ± 17.5	128.1 ± 18.3	<0.0001
Medical comorbidities			
Diabetes mellitus	1166 (2.8)	2898 (5.6)	<0.0001
Myocardial infarction	789 (1.9)	1517 (2.9)	<0.0001
Elevated cholesterol	5474 (13.1)	8299 (15.9)	<0.0001
Congestive heart failure	300 (0.7)	721 (1.4)	<0.0001
Cardiovascular disease	7206 (17.3)	10,317 (19.8)	<0.0001
Alcohol use			0.007
≥7 drinks per wk	5355 (12.9)	6349 (12.2)	
1 to <7 drinks per wk	10,574 (25.4)	13,250 (25.5)	
Others (nondrinker, past drinker, <1 drink per mo, <1 drink per wk)	25,386 (61.0)	32,077 (61.6)	
Cigarette smoking			<0.0001
Never smoked	20,426 (49.1)	26,595 (51.1)	
Former smoker	18,425 (44.3)	21,089 (40.5)	
Current smoker	2227 (5.3)	3563 (6.8)	

* The mean values are expressed ± SD.

In the unadjusted analysis, participants who reported active use of HRT were 60% more likely to suffer an SAH (RR 1.6, 95% CI 1.1–2.3) (Table 2). Adjustment for all potential confounders did affect the RR of SAH associated with active use of HRT. In the multivariate adjusted analyses, participants who reported active use of HRT were 50% more likely than those without HRT to suffer an SAH (RR 1.5, 95% CI 1.0–2.2). The risk of SAH was higher among women on “estrogen only” HRT (RR 1.4, 95% CI 0.91–2.0) than “estrogen and progesterone” HRT (RR 1.2, 95% CI 0.8–2.1). In another analysis, the RR of SAH was significantly lower among participants who had never used HRT compared with those who had used HRT

either in the past or were actively using HRT (HR 0.58, 95% CI 0.4–0.9).

Discussion

Use of HRT continues to be prevalent among postmenopausal women, with a lifetime prevalence of HRT ranging from 26.8% to 48%.¹⁷ Active use is reported by 24%⁵–32%¹⁷ of postmenopausal women. The prevalence is higher among younger postmenopausal women.^{5,17,20} The prevalence is either similar or lower among women who develop SAH. In a population-based study within Kings County, Washington, 25% of women with SAH were ei-

FIG. 1. Comparison of 10-year SAH-free survival in patients with active estrogen-only HRT, active any HRT, and no use of HRT.

ther actively using or had used HRT.¹⁹ In the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS), 21% of women with SAH had used or were actively using HRT.²² In an analysis of the Danish National Patient Register, 35% of Danish women 45–64 years of age with SAH had either used or were actively using HRT.²⁵

We found that the risk of SAH was 1.5-fold higher among postmenopausal women on HRT after adjusting for potential confounders. Both “estrogen only” and “estrogen and progesterone” HRT were associated with an increased risk for SAH. Our results may be different from

results of some of the previous case control studies.^{19,22} The increased risk in postmenopausal women is similar to the increased risk observed with oral contraceptive use in premenopausal women.¹¹ There was a 40% higher risk of SAH among women who used oral contraceptives in previous analyses.¹¹ High-estrogen oral contraceptives appeared to impart a greater risk than low-dose preparations in studies that controlled for smoking, but the difference was not significant. The combination of cigarette smoking and oral contraceptive use resulted in a synergistic increase in risk of SAH.²⁶ The unadjusted magnitude of absolute difference in rates of SAH between women on

TABLE 2. Multivariate adjusted risk of SAH in postmenopausal women using HRT: WHI Observational Study

Parameter	Total No. of Pts	No. of SAH Cases	Rate Per 100 Persons	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Active use at baseline evaluation					
Nonactive user of HRT	38,024	35	0.09	Reference	Reference
Active user of any HRT	41,630	58	0.1	1.6 (1.1–2.3)	1.5 (1.0–2.2)
Active user of “estrogen only” replacement therapy	23,290	37	0.2	1.4 (0.94–2.1)	1.4 (0.91–2.0)
Active user of “estrogen and progesterone” combination replacement therapy	18,340	21	0.1	1.4 (0.9–2.2)	1.2 (0.8–2.1)
Any lifetime use					
Used HRT at any time (past or active)	55,488	79	0.1	Reference	Reference
Never used HRT	38,024	35	0.09	0.57 (0.4–0.9)	0.58 (0.4–0.9)

pts = patients.

* Adjusted for age, systolic blood pressure, cigarette smoking, alcohol use, body mass index, ethnicity, diabetes mellitus, and cardiovascular disease.

HRT and those without HRT was small (0.14% vs 0.11%, or 0.03%). The magnitude of absolute difference was similar to the difference in rate of SAH observed in women with active cigarette smoking and those with no history of smoking (0.14% vs 0.11%, or 0.03%) in the WHI study. The clinical significance of such differences may not be adequate for acceptance of new therapeutic interventions for prevention of SAH that are associated with increased cost and risk, but may be of value in abstinence strategies that are associated with cost reduction, such as avoidance of HRT and cigarette smoking.

Endothelial and vascular smooth muscle cells are abundant with both estrogen receptor- α and estrogen receptor- β .^{12,35} Estrogens in both human studies and experimental models cause a significant alteration in vascular tone.²³ The antiinflammatory and vascular relaxation effect of estrogen is not seen after a prolonged period of estrogen deprivation,^{27,29} which may have a common occurrence in WHI participants who were 50–79 years of age and had a large interval between menopause and initiation of HRT. However, the mechanism underlying the increased risk associated with HRT is probably related to the complex relationship between the ratio of different types of estrogen receptors present in vascular smooth muscles and context specificity of the estrogen hormones.¹⁴ Estrogens produce reactive oxygen species by increasing mitochondrial activity and redox cycling of estrogen metabolites, leading to activation of proinflammatory pathways.³⁷ An increase in plasma fibrinolytic activity primarily related to a significant increase in tissue-type plasminogen activator and a decrease in plasminogen activator inhibitor Type 1 has been observed in women receiving HRT.^{9,32,36} Cerebral vasodilation⁴ and transient elevation in systemic blood pressure³¹ associated with HRT may additionally contribute to risk of SAH in postmenopausal women.

The results were obtained from a population 50–79 years of age, with only 28% of these women being between 50–59 years old.¹⁶ Younger and/or more recently menopausal women may have a better risk-benefit ratio than older or remotely menopausal women.¹⁰ The age distribution and delay in initiation of HRT after menopause may not accurately reflect the current practice. The class effects associated with particular estrogen and progesterone types were not investigated. Conjugated equine estrogens and 17 β -estradiol differ with respect to their source and composition, pharmacokinetic and metabolic profile, and total estrogenic potency.⁶ For progesterone, medroxyprogesterone acetate and norethisterone acetate have different pharmacokinetic profiles and different activities on steroid receptors. Therefore, generalization of results pertaining to certain HRTs must be undertaken with caution. The duration of treatment is another issue because of data suggesting that cardiovascular benefit of HRT may require at least 5 years of treatment.⁶

Conclusions

Postmenopausal women, particularly those at risk for SAH due to presence of unruptured aneurysms, family history, or cardiovascular risk factors, should be counseled against use of HRT. If the HRT use is medically necessary

in women who have risk factors for SAH, an estrogen and progesterone combination may be preferable rather than unopposed estrogen preparations.²¹

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Author Contributions

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