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Age at menopause, reproductive history and venous thromboembolism risk among postmenopausal women:

The Women's Health Initiative Hormone Therapy clinical trials

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Abstract

Objectives—To investigate VTE risk in relation to age at menopause, age at menarche, parity, bilateral oophorectomy and time since menopause, as well as any interaction with randomized HT assignment among postmenopausal women.

Methods—Using pooled data from the Women's Health Initiative HT clinical trials including 27,035 postmenopausal women ages 50 to 79 years with no history of VTE, we assessed the risk of VTE in relation to age at menopause, age at menarche, parity, bilateral oophorectomy and time since menopause by Cox proportional hazard models. Linear trends, quadratic relationships and interactions of reproductive life characteristics with HT on VTE risk were systematically tested.

Results—During the follow-up, 426 women reported a first VTE, including 294 nonprocedure-related events. No apparent interaction of reproductive life characteristics with HT assignment on VTE risk was detected and there was any significant association of VTE with age at menarche, age at menopause, parity, oophorectomy or time since menopause. However, analyses restricted to nonprocedure-related VTE showed a U-shaped relationship between age at menopause and thrombotic risk that persisted after multivariable analysis ($p < 0.01$). Compared to women aged 40 to 49 years at menopause, those with early menopause (age < 40 years) or with late menopause

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(age>55 years) had a significant increased VTE risk (HR=1.8;95%CI:1.2–2.7 and HR=1.5;95%CI: 1.0–2.4, respectively).

Conclusion—Reproductive life characteristics have little association with VTE and do not seem to influence the effect of HT on thrombotic risk among postmenopausal women. Nevertheless, early and late onset of menopause might be newly identified risk factors for nonprocedure-related VTE.

Keywords

age at menopause; venous thromboembolism; risk factors

Introduction

Cardiovascular disease (CVD) is the leading cause of death among women in developed countries¹. Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important contributor to CVD burden^{2, 3}, with an incidence of about 1 per 1,000 person-years among postmenopausal women⁴ and lead to a fatal outcome for approximately 10% of cases⁵. Identifying women at high thrombotic risk is of great importance for CVD prevention.

Women are subject to endogenous and/or exogenous estrogen exposure throughout life, from puberty to menopause but also after menopause. Exogenous estrogens, including hormonal contraceptives and postmenopausal hormone therapy (HT), have been shown to be related to thrombotic risk^{6–8}. This association may depend on several factors, including the route of estrogen administration^{9–14}, estrogen doses^{12, 15} and formulation¹⁶ and type of progestogens^{10, 11, 15, 17, 18}. Whereas characteristics of reproductive life have been related to arterial disease^{19–25}, as well as cancer^{26–28} and mortality^{23, 29–34}, indicators of lifetime endogenous estrogen exposure have been less investigated in relation to VTE in postmenopausal women and with conflicting reports^{35–39}. In addition, data on a potential interaction of HT use with the different reproductive life characteristics on postmenopausal VTE risk are quite limited³⁹. The Women's Health Initiative (WHI) HT clinical trials provided the opportunity to investigate the association of VTE with age at menarche, age at menopause, parity, bilateral oophorectomy and time since menopause, as well as any potential interaction of HT use with these characteristics on VTE risk among postmenopausal women.

Methods

Study population

The WHI HT clinical trials were designed to test the effects of postmenopausal HT on a variety of health outcomes among healthy postmenopausal women, as has been described in detail elsewhere^{2, 3, 40}. Briefly, 27,347 postmenopausal women ages 50 to 79 years were recruited between 1993 and 1998 at 40 US clinical centers, including 16,608 with an intact uterus at baseline who were randomly assigned to receive either 0.625 mg/day conjugated equine estrogens (CEE) plus 2.5 mg/day medroxyprogesterone acetate or matching placebo (E+P trial) and 10,739 hysterectomized women who were assigned to either 0.625 mg/day CEE or placebo (E-alone trial). Before treatment assignment, a 3-month washout period was required for women who were current HT users at the initial screening (n=815 for E+P trial and n=1128 for E-Alone trial, respectively). All women provided written informed consent at enrollment and completed a series of self-administered baseline questionnaires from which detailed data on socio-demographic factors, characteristics of reproductive life, personal and family medical history, medication use and lifestyle were collected. Systolic

and diastolic blood pressure, weight and height were measured at baseline clinic visits. For the present analysis, women with a personal history of VTE at baseline (n=312) were excluded, resulting in a cohort of 27,035 postmenopausal women.

Exposure assessment and baseline covariates

Menopausal status was defined as either no vaginal bleeding for 12 months (6 months for women older than 55 years old), hysterectomy more than 3 months before or use of postmenopausal HT. HT use was defined at baseline and a 3-month washout period was required for women using hormone at the initial screening. Age at menopause was then defined as the age of last menstrual bleeding or use of postmenopausal HT. Menarche was defined as the first menstrual period and parity as the number of term pregnancies. Bilateral oophorectomy was the removal of both ovaries. Age at menarche, age at menopause, parity and bilateral oophorectomy were self-reported on baseline questionnaires. Body-mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and analyzed as a continuous variable. Smoking status was studied in two categories (non smoking or current smoking) and total MET score as a continuous variable based on reported physical activity⁴¹. Hypertension status was defined as high blood pressure measurement (systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more) and/or current use of antihypertensive medication. A woman was considered diabetic if she reported use of an antidiabetic medication or had answered yes to the question “Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?”. Hypercholesterolemia was defined as the use of lipid-lowering treatment. History of events at baseline were self-reported and consisted of cancers, stroke, transient ischemic attack and coronary heart disease including myocardial infarction, angina pectoris, coronary artery bypass and percutaneous transluminal coronary angioplasty.

VTE event ascertainment

Participants were followed-up for clinical events every 6 months and had an annual in-clinic visit^{2, 3}. VTE events were defined as deep vein thrombosis (DVT) or pulmonary embolism (PE) that occurred between randomization date and the end of treatment assignment (2002 for the E+P trial and 2004 for the E-alone trial). Each possible event was reviewed by a local physician and then centrally adjudicated by review of medical records. Diagnosis of DVT required documentation of a treating physician’s diagnosis and positive findings of Doppler or duplex ultrasound, venogram, plethysmography, or isotope scan. PE was based on a hospital discharge summary with a PE diagnosis and positive results on ventilation-perfusion lung scan, pulmonary angiogram or computed tomography. PE was also confirmed if signs and symptoms suggested PE in the presence of a documented DVT. Venous thrombotic events were further classified as procedure-related if they occurred within 60 days after an invasive procedure or as nonprocedure-related otherwise. This classification that referred to codes 997.3 (Respiratory complications resulting from a procedure) and 997.2 (Phlebitis and thrombophlebitis during or resulting from a procedure) of the International Classification of the Disease version 10 was adjudicated by a local physician and centrally confirmed by a medical committee. During the follow-up, 426 first VTE events were validated (317 DVT and 208 PE), including 294 nonprocedure-related events (222 DVT and 144 PE). There were 30 cases that could not be classified as either procedure-related or nonprocedure-related VTE.

Statistical analysis

Cox proportional hazard models with delay as the time scale were used to assess the hazards ratios (HR) and corresponding 95% confidence interval (CI) for VTE in relation to age at menarche, age at menopause, parity, bilateral oophorectomy and time since menopause.

Each model presented met the proportional hazards assumption. The time-to-event for VTE event was the number of days from randomization to the first diagnosis. Otherwise, the censoring time was the time from randomization to the earliest date of death, loss to follow-up or end of treatment assignment. Potential interactions between each characteristic of reproductive life and treatment assignment (i.e. placebo or active treatment in the E+P or E-alone trials) on the VTE risk were systematically tested. As no significant interaction was detected, we performed pooled analyses with adjustment for the randomization status. Further adjustment included age, BMI, race, history of events, smoking status, total MET-score, hormone use at baseline and its duration. The linearity of the associations of VTE with characteristics of reproductive life was systematically assessed. When the linearity of the models was confirmed, linear trend across the different categories of each characteristic of reproductive life was tested. For models which deviated from the linearity, nonlinear (U-shaped) relations were assessed with the use of quadratic terms in the Cox models.

Primary analysis focused on overall first VTE including both nonprocedure-related and procedure-related events. Then, subgroup analyses were specifically conducted for nonprocedure-related VTE. Cases of procedure-related VTE were thus censored as non-cases at the time of event and women with VTE that could not be classified were excluded from the analysis. Finally, stratified analyses were performed according to the type of events (DVT or PE).

Results

The table 1 shows the baseline general characteristics of the 27,035 postmenopausal women with no history of VTE at baseline included in the present analysis. Mean of follow-up was 6.2 years (SD=1.6 years). Women were 63.4 years old on average and mean BMI was 29.1 kg/m². More than 50% of the participants had one or more of the following comorbidities: diabetes, hypertension, hypercholesterolemia, personal history of cancer or cardiovascular disease. Mean age at menarche and menopause was 12.6 and 47.9 years, respectively, and average number of children among the 90% of the multiparous women was 3.2. About 25% of women previously had a bilateral oophorectomy at baseline.

The table 2 shows the HR and 95% CI of first VTE event in relation to HT assignment versus placebo by characteristics of reproductive life. No interaction of these characteristics with treatment assignment on VTE risk was detected. Therefore, pooled analyses with adjustment for the treatment assignment were performed to assess the risk of VTE by reproductive life characteristics.

Table 3 shows the risk of first VTE event by reproductive life characteristics. There were no significant associations of VTE with age at menarche, age at menopause, parity, baseline bilateral oophorectomy or time since menopause. However, analyses restricted to nonprocedure-related VTE showed a U-shaped relationship between age at menopause and thrombotic risk that persisted after multivariable analysis (p for quadratic association <0.01, table 4). Compared to women with age at menopause between 40 and 49 years, those with early menopause (age<40 years) and with late menopause (age>55 years) had a significant increased VTE risk (Adjusted HR=1.8; 95%CI: 1.2–2.7 and HR=1.5; 95%CI: 1.0–2.4, respectively). Separate analysis for DVT yielded similar results and showed an increased thrombotic risk among women with early and late menopause (HR=1.8; 95%CI: 1.2–2.8 and HR=1.6; 95%CI: 1.0–2.7, respectively, p for quadratic association=0.01) while this association missed the statistical significance for PE (HR=1.2; 95%CI: 0.6–2.0 for women with menopause before 40 years and HR=1.6; 95%CI: 0.8–2.9 for women with menopause after 55 years, p for quadratic association=0.33). With respect to other characteristics of reproductive life, restricted analysis to nonprocedure-related VTE did not show a significant

association of VTE (Table 4). Using participants with age at menarche less than 12 years as the reference group, women who had their first periods between 12 and 14 and those with first periods after 14 years had a similar VTE risk (HR=1.0; 95%CI: 0.8–1.4 and HR=1.0; 95%CI: 0.7–1.6, respectively). Regarding parity, women with 1 or 2 children, women with three or 4 children and those with 5 or more children had VTE risk similar to nulliparous women (HR=1.0; 95%CI: 0.6–1.6, HR=1.1; 95%CI: 0.7–1.7 and HR=1.0; 95%CI: 0.6–1.7, respectively). Finally, neither baseline bilateral oophorectomy nor time since menopause had a significant influence on the risk of nonprocedure-related VTE.

Finally, stratified analysis on the presence of comorbidities at baseline led to similar results as those obtained in the overall population for both total VTE and nonprocedure-related events.

Discussion

To our knowledge, this is the first study to show a U-shaped association between the age at menopause and the risk of nonprocedure-related VTE among postmenopausal women who had never had a previous history of VTE. After adjustment for potential confounders, women who experienced menopause before 40 years or after 55 years had an increased thrombotic risk as compared to women with age at menopause between 40 and 49 years. In contrast, this study suggests there is no association of VTE with age at menarche, parity, bilateral oophorectomy or time since menopause. In addition, there was no apparent interaction of HT use with these reproductive life characteristics on VTE risk.

Characteristics of reproductive life have been studied primarily in relation to coronary events and mortality, but few studies have investigated the association of VTE with markers of lifetime endogenous sex steroid hormones among postmenopausal women.

The VTE risk by age at menopause has been assessed in four studies^{35, 37–39}. In the Heart and Estrogen/progestin Replacement Study clinical trial, Grady et al. found that an age older than 52 years at the last menstrual period was independently associated with a higher risk of VTE³⁵. Later, Simon et al. confirmed this result in a case-control study of idiopathic VTE. They showed that, independently of BMI, women with late menopause had a higher thrombotic risk than did women with normal menopause³⁷. Our data showing an increased risk of nonprocedure-related VTE with an older age at menopause are concordant with these previous results. More recently, early menopause, which had been consistently associated with coronary heart disease and stroke^{22, 31, 42}, has been found to be independently related to an increased thrombotic risk in postmenopausal women³⁸. Our findings showing that early menopause was associated with an increased VTE risk are in agreement with these latest findings. Finally, our data are consistent with the results of a recent study showing an increased VTE risk among women with early and late menopause, even though that association missed the statistical significance in their study³⁹.

Previous data regarding the relationship between parity and thrombotic risk among postmenopausal women are conflicting. While two case-control studies found that high parity was associated with an increased VTE risk independently of BMI^{36, 37}, two recent cohorts supported our findings of no association^{38, 39}. Similarly, results regarding the relationship between parity and arterial events have been inconclusive^{33, 43–46}.

Research on the relationship between age at menarche and cardiovascular disease has been limited^{23, 43, 47}. Our data are the first to focus on the risk of VTE. Overall, early menarche seems to be deleterious for arterial events and mortality^{23, 34, 43, 47–49}. Investigations of the impact of surgical menopause on VTE risk have been limited. Two studies showed no significant associations of VTE with surgical menopause^{9, 39}, as we report here. Another

epidemiological study of VTE reported an increased thrombotic risk among women with bilateral oophorectomy which was no longer statistically significant after adjusting for confounding variables, including BMI⁵⁰.

To our knowledge, time since menopause has not been investigated in relation to VTE risk previously; however, it was recently studied in relation to arterial disease, with a finding of no significant association with coronary heart disease or stroke⁵¹. Nevertheless, time since menopause has been positively related to cardiovascular risk factors⁵² and all-cause mortality⁵³.

Finally, there are few data available regarding a potential interaction of HT use with the different characteristics of reproductive life. One recent study concurred with our findings that the associations of HT use with incident VTE did not differ among the categories of parity and type of menopause³⁹. In addition, there is evidence for an interaction of HT use with time since menopause on arterial disease among postmenopausal women⁵⁴. However, the effect of HT use on VTE risk has not to date been investigated by time since menopause^{55, 56}.

The existence of an independent association between age at menopause and VTE risk among postmenopausal women does not prove causality. The association of early menopause with an increased thrombotic risk could be partly explained by specific characteristics and/or comorbidities of women who experienced a premature menopause. Indeed, early menopause could reflect a general adverse health status⁴² and could be the result of an accelerated aging process which would involve multiple tissues and organs including ovaries³¹. This biological process would lead to a premature cessation of ovarian activity but also to an increase in the incidence of age-related pathologies including arterial and venous disease²². Under this hypothesis, the hormonal changes observed among women with early menopause would have no causal effect on the occurrence of VTE but cessation of ovarian activity and increase in VTE incidence could both be consequences of an accelerated aging process among these women. On the other hand, increase in VTE risk could also be due to direct biological mechanisms, including a prothrombotic state, decreased blood flow, and/or an alteration of the vessel wall⁵⁷. In particular, older age at menopause involves a longer exposure to both endogenous estradiol and progesterone. It could be hypothesized that the presence of both estrogen and progesterone receptors on the venous wall⁵⁸ could underly possible deleterious effects of long-term estrogen and/or progesterone exposure on blood flow leading to venous damage. On the other hand, procoagulant mechanisms or haemostatic activation could also be implicated in the association of age at menopause with thrombotic risk remains unknown.

The WHI HT clinical trials have several strengths. The WHI is a large, geographically diverse, multi-ethnic U.S. cohort of postmenopausal women for whom baseline data were collected by standardized procedures and included detailed questionnaires with information on many key characteristics of reproductive life, as well as many potential confounding factors that could be included in the statistical analysis. In particular, the general characteristics of women differed according to their age at menopause but adjustment for these baseline factors, including BMI, did not modify the results. Finally, VTE events were carefully validated by a central adjudication committee using criteria focused on imaging procedures.

Despite these strengths, the WHI study has some limitations which deserve consideration^{2, 3}. For the present analysis, an important limitation pertains to the self-reported information on characteristics of the reproductive life that could lead to misclassification. Such misclassification is likely to be non-differential and would lead to an underestimation of the

true relationships, which could explain the non-significant association of VTE with age at menarche or time since menopause. Another limitation is that characteristics of reproductive life are only surrogate markers of lifetime endogenous estrogen exposure and may not reflect results derived from direct measurement of endogenous sex steroid hormone levels in relation to VTE risk. In addition, these findings referred to postmenopausal women who agreed to participate in the WHI HT clinical trials so the result needs to be cautiously extrapolated to the general population of postmenopausal women. Finally, stratified analyses include subgroups with relatively low number of cases, especially for PE, and resulted in low statistical power.

Conclusion

In conclusion, early and late menopause could emerge as newly identified risk factors for VTE among postmenopausal women. Since VTE may cause significant disability and/or death, identifying new risk factors could improve risk stratification and disease prevention, especially for populations at high thrombotic risk. Future research should address VTE risk in relation to specific endocrine profiles of women with early or late menopause to elucidate biological mechanisms that could be involved in these relationships. Furthermore, a possible implication is that women with premature menopause, who could be at high VTE risk, should avoid oral estrogen therapy. Although observational studies have suggested that transdermal estrogen, with or without a progestogen, may be a safer option with respect to VTE risk, additional research is needed.

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Table 1

Baseline general characteristics of women without a personal history of VTE included in the Women's Health Initiative clinical trials (n=27,035).

Characteristics	Value
Age (years)	63.4 (7.2)
Ethnicity	
White	21,752 (80.5)
Black	2,719 (10.1)
Hispanic	1,527 (5.6)
American Indian	129 (0.5)
Asian/Pacific Island	526 (1.9)
Unknown/others	382 (1.4)
Body-mass index (kg/m²)	29.1 (6.0)
Medical history	
Diabetes	2,013 (7.5)
Hypertension	11,372 (42.1)
Hypercholesterolemia	3,589 (14.7)
Current smoking	2,801 (10.5)
Total energy expenditure (METs-hour/week)	10.8 (13.2)
Prevalent disorders	
Coronary heart disease	1,762 (6.6)
Stroke or Transient ischemic attack	807 (3.0)
Cancer	862 (3.2)
Randomization status	
Estrogen only	5,223
Placebo for Estrogen only	5,345
Estrogen plus progestin	8,427
Placebo for Estrogen plus Progestin	8,040
Age at menarche (years)	12.6 (1.5)
Age at menopause (years)	47.9 (6.6)
Parity	
Never pregnant/never had pregnancy term	2,624 (9.8)
At least one children	24,266 (90.2)
number of children (n)	3.2 (1.3)
Bilateral oophorectomy	6,666 (25.1)
Time since menopause (years)	15.6 (9.4)

Data are given as n (%) or arithmetic means (SD)

Table 2

Adjusted* hazard ratios and 95% confidence interval of first VTE event in relation to HT use versus placebo by characteristics of reproductive life within each trial

	E+P trial					E-alone trial					<i>p</i> for interaction	
	HT users		Placebo users			HT users		Placebo users				
	Number of women	Number of cases	Number of women	Number of cases	Adjusted HR *	Number of women	Number of cases	Number of women	Number of cases	Adjusted HR *		
Age at menarche (years)												
<12	1715	36	1654	12	3.0 (1.5 – 6.2)	1189	29	1260	16	1.8 (1.0 – 3.4)	0.52	
12–14	5760	109	5486	57	2.0 (1.4 – 2.8)	3478	66	3486	56	1.1 (0.8 – 1.6)		
>14	931	15	864	6	3.3 (1.1 – 10.3)	525	12	577	11	1.3 (0.6 – 3.0)		
Age at menopause (years)												
<40	194	4	185	3	1.3 (0.3 – 5.8)	1003	24	1086	20	1.1 (0.6 – 2.1)	0.51	
40–49	2597	34	2611	23	1.5 (0.9 – 2.5)	2091	41	2121	27	1.4 (0.8 – 2.3)		
50–55	4178	94	4033	34	2.7 (1.8 – 4.1)	1057	16	1068	16	0.9 (0.4 – 2.0)		
>55	645	14	624	5	2.4 (0.9 – 6.9)	276	8	288	4	2.6 (0.7 – 9.9)	0.15	
Parity												
Nulliparous	854	11	829	9	1.0 (0.4 – 2.6)	486	7	455	7	0.9 (0.3 – 2.6)		
1 or 2	2574	49	2354	19	3.2 (1.8 – 5.8)	1431	26	1544	13	2.0 (1.0 – 4.1)		
3 or 4	3411	70	3334	31	2.5 (1.6 – 4.0)	2089	48	2161	40	1.3 (0.8 – 1.9)		
5 or more	1552	28	1488	16	1.5 (0.8 – 3.0)	1177	26	1151	23	1.1 (0.6 – 2.0)		
Baseline bilateral oophorectomy												
No	8011	150	7646	70	2.3 (1.7 – 3.1)	2132	40	2065	38	1.0 (0.6 – 1.6)	0.37	
Yes	376	8	365	5	2.0 (0.6 – 6.5)	2867	62	3058	43	1.5 (1.0 – 2.3)		
Time since menopause (years)												
<10	2758	33	2694	10	3.4 (1.6 – 7.2)	817	9	802	8	1.1 (0.4 – 2.9)	0.80	
10–19	3019	62	2969	31	1.9 (1.2 – 2.9)	1408	24	1477	21	1.1 (0.6 – 2.0)		
>20	1837	51	1790	24	2.1 (1.3 – 3.5)	2202	56	2284	38	1.4 (0.90 – 2.1)		

* Adjusted for age, BMI, race, history of events, smoking status, total energy expenditure, hormone use at baseline and its duration

Table 3

Hazard ratios and 95% Confidence Intervals of first VTE event by reproductive life characteristics in women included in the Women's Health Initiative clinical trials

Characteristics	Number of women n=27,035	Number of cases n=426	Adjusted HR (95% CI)
Age at menarche (years)			
<12	5,818	93	1 (reference)
12–14	18,210	288	1.1 (0.8 – 1.4)
>14	2,897	44	1.1 (0.7 – 1.6)
<i>p for linear trend</i>			0.70
Age at menopause (years)			
<40	2,468	51	1.5 (1.0 – 2.1)
40–49	9,420	125	1 (reference)
50–55	10,336	160	1.2 (0.9 – 1.5)
>55	1,833	31	1.1 (0.7 – 1.7)
<i>p for linear trend</i>			0.74
Parity			
Nulliparous	2,624	34	1 (reference)
1 or 2	7,903	107	1.1 (0.7 – 1.6)
3 or 4	10,995	189	1.3 (0.9 – 1.9)
5 or more	5,368	93	1.1 (0.7 – 1.7)
<i>p for linear trend</i>			0.34
Baseline bilateral oophorectomy			
No	19,854	298	1 (reference)
Yes	6,666	118	1.0 (0.7 – 1.3)
Time since menopause (years)			
<10	7,071	60	1 (reference)
10–20	8,873	138	0.3 (0.9 – 1.8)
>20	8,113	169	1.3 (0.8 – 2.0)
<i>p for linear trend</i>			0.34

HR: Hazard ratio; 95%CI: 95% Confidence Intervals

Adjusted for BMI, age, race, history of events, total energy expenditure, smoking status, HT arms, hormone use at baseline and its duration

Table 4

Hazard ratios and 95% Confidence Intervals of first non-procedure-related VTE event by reproductive life characteristics in women included in the Women's Health Initiative clinical trials

Characteristics	Number of women n=27,005	Number of cases n=294	Adjusted HR (95% CI)
Age at menarche (years)			
<12	5,813	65	1 (reference)
12–14	18,186	197	1.0 (0.8 – 1.4)
>14	2,896	31	1.0 (0.7 – 1.6)
<i>p for linear trend</i>			<i>0.91</i>
Age at menopause (years)			
<40	2,467	39	1.8 (1.2 – 2.7)
40–49	9,411	82	1 (reference)
50–55	10,325	109	1.2 (0.9 – 1.7)
>55	1,833	28	1.5 (1.0 – 2.4)
<i>p for U-shaped</i>			<i><0.01</i>
Parity			
Nulliparous	2,621	28	1 (reference)
1 or 2	7,897	77	1.0 (0.6 – 1.6)
3 or 4	10,982	123	1.1 (0.7 – 1.7)
5 or more	5,360	63	1.0 (0.6 – 1.7)
<i>p for linear trend</i>			<i>0.75</i>
Baseline bilateral oophorectomy			
No	19,830	209	1 (reference)
Yes	6,660	78	0.9 (0.7 – 1.3)
Time since menopause (years)			
<10	7,068	41	1 (reference)
10–20	8,866	96	1.2 (0.8 – 1.9)
>20	8,102	121	1.3 (0.8 – 2.1)
<i>p for linear trend</i>			<i>0.42</i>

HR: Hazard ratio; 95%CI: 95% Confidence Intervals

Adjusted for BMI, age, race, history of events, total energy expenditure, smoking status, HT arms, hormone use at baseline and its duration