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ORIGINAL ARTICLE

Observational Study

Variation in use of menopausal hormone treatment on risk of health outcomes

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Conflict-of-interest statement: Both authors declare no conflict of interest in the findings of the study.

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Abstract

AIM: To determine the relative risk of selected serious outcomes with variations in use of menopausal hormone treatment (MHT).

METHODS: A cohort of 489 women, randomly recruited at age 40-79 years, from a longitudinal study of urbanised population was a study group and was followed for 14 years. Four selected outcomes (coronary artery disease, stroke, peripheral artery disease, breast cancer) were tested. Each woman on entry to the study was interviewed by a dedicated medical practitioner, and data on menstrual and menopausal history and health status were obtained. Outcome information was ascertained by questionnaire and medical reports from attending medical practitioners. In case of death, cause of death was checked with the Registry of Births, Deaths, Marriages and Divorce. This information was available for all women. An ever-user of MHT was defined as use for 6 mo or more at any time during the study. A late start of MHT was defined as 3 years or more from onset of menopause. The generalised linear statistical package was used to examine the data; univariate logistic regression models were used to describe the relationship between patient characteristics and a disease outcome, followed by stepwise multi variate analysis, controlling for age, lifestyle factors and co-morbidities.

RESULTS: The risk of ever-use of MHT was significantly increased only for peripheral artery disease (RR = 2.16; 0.99, 4.71; P = 0.05), and not for coronary artery disease, stroke and breast cancer. A late start of MHT (three years or more from onset of menopause) was

associated with significantly increased risks for coronary artery disease (RR = 2.56; 1.15, 5.72; *P* = 0.02) and peripheral artery disease (RR = 4.42; 1.55, 12.64; *P* = 0.005), and use after age 60 years with significantly increased risks for coronary artery disease (RR = 4.98; 2.19, 11.55; *P* < 0.001), stroke (RR = 2.99; 1.11, 8.08; *P* = 0.03) and peripheral artery disease (RR = 4.18; 1.24, 14.14; *P* = 0.02). Use up to 10 years was not associated with significant risk for all outcomes. These risks were confirmed by stepwise multi variate analysis, adjusting for age at recruitment, body mass index, smoking, physical activity and alcohol use, and existing diabetes, mellitus, hypertension and hypercholesterolaemia. Regardless of variations in use, risk for breast cancer was not found.

CONCLUSION: The study confirms ever-use of MHT affected only risk of peripheral artery disease; but some use variations could have adverse effects.

Key words: Menopausal hormone treatment; Variation in use; Risk outcomes

Core tip: In contrast to larger studies, this small observational study examined effects of various ways of use of menopausal hormone treatment (MHT) when given for clinical indications. Of the four selected outcomes available at 14 years follow-up, overall risk was only increased for peripheral artery disease but not for coronary artery disease, stroke and breast cancer. However, risk was increased for coronary artery disease and peripheral disease when MHT was started more than three years after menopause in women over 60 years.

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INTRODUCTION

Since the findings of the Women's Health Initiative (WHI) were reported in 2002, there has been considerable research activity in analyses, re-analyses and meta-analyses of available and new data on the risks of use of hormone therapy at and after menopause. The reason for termination of the combined oestrogen plus progestogen arm of the WHI was a significant increase in risk of several health outcomes, namely breast cancer, coronary artery disease, stroke and deep vein thrombosis[1]. However, the reason for termination of the oestrogen-only arm of the same study, was different - the increase in risk was only significant for one outcome - stroke - and the risks of breast cancer and coronary artery disease were not increased[2]. Other studies such as the Million Women Study (MWS)[3] and the California Teachers Study[4], have added more information to an emerging complex plethora of data which gives rise to a variety of opinions and recommendations from international expert bodies. An excellent and comprehensive review of the risks and benefits of use is given by Davey[5].

Much attention has been given to obtain a better understanding of the vascular risks, especially in the heart and brain, and to reconcile the differences in outcomes of menopausal hormone treatment (MHT) between observational and randomised controlled studies. Lessons from monkey models suggest variable effects due to timing of treatment[6]. Whereas surgically-induced oestrogen deficiency results in premature coronary artery atherosclerosis, the process is prevented when replacement oestrogen is given early but not so when given late after the deficiency. This is the concept of a "window of opportunity" to explain the variable findings in women. It is proposed that oestrogen has a beneficial effect on arteries in younger women by preventing or delaying atherosclerosis; but when given to older women with advanced plaque formation, the effect may be absent or even, deleterious. However, the Kronos Study failed to show a good effect[7], whilst a Danish Study reported reduced risk of mortality and myocardial infarction[8].

In view of these variable findings, clinicians need to be aware that MHT may have different effects and risk outcomes when given in different ways and at different times of the woman's life. In this study, the effects of variations in use of MHT were tested in a cohort of women from a Longitudinal Study of Ageing in Women (LAW Study). Use variations included ever-use, timing of initiation of treatment from menopause, types of regimen, age at start or stopping treatment, and duration of treatment. The outcomes selected for their clinical importance included coronary artery disease, stroke, peripheral artery disease and breast cancer. We report the findings after 14 years of follow-up.

MATERIALS AND METHODS

The women in this study belonged to a cohort who have been recruited for a multidisciplinary longitudinal study on ageing and to date, follow-up has reached 14 years. The design and recruitment procedures of the overall study have been previously described[9]. Approval was given by the Ethics Committee of the Royal Brisbane and Women's Hospital. Informed consent was also obtained from all women recruited into the overall Study.

The cohort was recruited by random invitation from the electoral roll, based on age stratification into four age-decades: 40-49 years, 50-59 years, 60-69 years and 70-79 years. Each woman on entry to the study was interviewed by a dedicated medical practitioner on an annual basis. In addition to other specific questions

Table 1 Distribution of outcomes and variation of use of menopausal hormone therapy in study cohort

	No. of women			
	Never-users		Ever-users	
No. of events during 14 yr follow-up (% in group)				
Coronary artery disease	33	(11.5%)	29	(14.3%)
Stroke	23	(8.0%)	19	(9.4%)
Peripheral arteria disease	10	(3.5%)	19	(9.4%)
Breast cancer	20	(6.9%)	12	(5.9%)
Timing of initiation of therapy from onset of menopause				
"Early start" (≤ 3 yr)	-		162	(80.2%)
"Late start" (> 3 yr)	-		40	(19.8%)
Type of regimen				
Oestrogen-only	-		30	(14.8%)
Oestrogen + progestogen	-		168	(83.2%)
Tibolone	-		4	
Combination of treatment strategy				
Early start plus oestrogen-only	-		20	(9.9%)
Early start plus oestrogen + progestogen	-		140	(69.3%)
Late start plus oestrogen-only	-		10	(4.9%)
Late start plus oestrogen + progestogen	-		28	(13.9%)
Other			4	
Age of patient when treatment started				
20-39 yr	-		17	(8.4%)
40-49 yr	-		85	(42.0%)
50-59 yr	-		82	(40.6%)
60-69 yr	-		18	(8.9%)
70-79 yr	-		17	(8.4%)
Age of patient when treatment stopped				
20-39 yr	-		0	
40-49 yr	-		20	(9.9%)
50-59 yr	-		85	(42.1%)
60-69 yr	-		69	(34.1%)
70-79 yr	-		28	(13.9%)
Duration of use (yr)				
< 1	-		15	(7.4%)
1-5	-		67	(33.2%)
6-10	-		37	(18.3%)
11-15	-		45	(22.3%)
16-20	-		19	(9.4%)
21-25	-		11	(5.4%)
> 25	-		7	(3.4%)
Total No. of women	287		202	

and assessments required by the other projects, information was obtained on use of MHT to include detailed menstrual and menopausal history and health status. Follow-up was continued by questionnaires on an annual basis to ascertain use of MHT, menopausal status as well as development of serious health outcomes, as determined by the attending medical practitioner. In particular, coronary artery disease, stroke, peripheral artery diseases (including carotid, femoral and popliteal arteries) and breast cancer were specifically ascertained. In women in whom information was uncertain, confirmation was made by direct contact with the attending medical practitioner. If death had occurred, cause of death was checked with the Registry of Births, Deaths, Marriages and Divorce, Department of Justice and Attorney-General, Queensland.

An ever-user of MHT was defined as a woman who had used MHT for 6 mo or more at any time during the study period of 14 years.

A cut-off time of three years was used to define timing of initiation of MHT in relation to onset of menopause. An "early start" user was a woman who had started within three years of onset of menopause; a "late start" user was one who had started MHT more than three years after menopause.

Statistical analysis

The analysis was revised and performed by a Biomedical Statistician (co-author: Lee Tripcony). The generalised linear statistical package (GLIM4) was used to examine the data. Univariate logistic regression models were used to describe the relationship between patient characteristics and a disease outcome. Variations in use of MHT analysed were used by patient (never-user, ever-user), timing of initiation of treatment in relation to onset of menopause (never "early start", "late start"), type of regimen (never, oestrogen-only, oestrogen plus progestogen), age of starting or stopping treatment (in categories), and duration of use (in categories). The dependent variables or outcome events were coronary artery disease, stroke, peripheral artery disease, and breast cancer. Hazard ratios with 95%CIs and *P* values were constructed. A *P* value ≤ 0.05 (two-sided) was taken to represent a significant association. From these results, only factors that had a *P* value < 0.1 were included in the stepwise construction of the multivariate model. Lifestyle and other factors fitted to the model included age at recruitment, body mass index, alcohol use, physical activity, smoking, and existing conditions at entry to study (diabetes mellitus, hypertension and hypercholesterolaemia).

RESULTS

There were 489 women in the cohort. Their ages in the two groups were comparable: 202 ever-users with mean age of 61.0 years (range 44-79; 95%CI: 59.9-62.0) and 287 never-users with mean age of 57.9 years (range 41-80; 95%CI: 56.4-59.3).

As shown in Table 1, the difference in the incidence of the four outcomes between never-users and ever-users was greatest for peripheral artery disease (3.5% *vs* 9.4%) and least for breast cancer (6.9% *vs* 5.9%).

Interestingly, 19.8% of women started MHT more than three years after menopause; 17.3% started MHT when aged 60 years or more, and 48.0% stopped MHT after age 60 years or more. There was a wide range of duration of use; 33.2% had used MHT for 1-5 years, another 50.0% for 6-20 years. Surprisingly, there were 8.9% of women who had used MHT for more than 20 years.

As expected, the majority (80.2%) of ever-users started treatment within 3 years of menopause, but there was still 19.8% who started late (17 women started MHT at age 70 years or more). A sub-group of 30 women had a hysterectomy and removal of both

Table 2 Menopausal hormone treatment and risk of serious outcomes: Ever-use, timing of initiation of treatment and type of regimen

	Relative risk estimate (95%CI)			
	Coronary artery disease	Stroke	Peripheral artery disease	Breast cancer
Ever-use	1.29 (0.76, 2.20) $P = 0.35$	1.14 (0.61, 2.14) $P = 0.69$	2.16 (0.99, 4.71) $P = 0.05$[1]	0.84 (0.40, 1.76) $P = 0.65$
Timing of initiation from onset of menopause				
Early start	1.02 (0.56, 1.86) $P = 0.94$	1.04 (0.52, 2.06) $P = 0.92$	1.65 (0.69, 3.94) $P = 0.26$	0.97 (0.45, 2.08) $P = 0.94$
Late start	2.57 (1.15, 5.72) $P = 0.02$[1]	1.57 (0.56, 4.37) $P = 0.39$	4.42 (1.55, 12.64) $P = 0.0052$	0.34 (0.05, 2.37) $P = 0.28$
Type of regimen				
Oestrogen only	2.34 (0.93, 5.88) $P = 0.07$	0.78 (0.18, 3.49) $P = 0.75$	5.01 (1.62, 15.48) $P = 0.005$	2.05 (0.65, 6.46) $P = 0.22$
Oestrogen + progestogen	1.16 (0.65, 2.06) $P = 0.62$	1.23 (0.64, 2.37) $P = 0.53$	1.59 (0.67, 3.79) $P = 0.30$	0.67 (0.29, 1.55) $P = 0.35$
Combination of treatment strategy				
Early start plus oestrogen-only	2.57 (0.88, 7.52) $P = 0.09$	1.22 (0.27, 5.56) $P = 0.80$	1.32 (0.16, 10.78) $P = 0.80$	2.36 (0.64, 8.72) $P = 0.20$
Early start plus oestrogen + progestogen	0.86 (0.44, 1.66) $P = 0.65$	1.03 (0.50, 2.12) $P = 0.94$	1.72 (0.70, 4.26) $P = 0.24$	0.81 (0.35, 1.89) $P = 0.62$
Late start plus oestrogen-only	1.92 (0.39, 9.45) $P = 0.42$	NC	16.73 (4.12, 67.91) $P < 0.001$[2]	1.48 (0.18, 12.29) $P = 0.71$
Late start plus oestrogen + progestogen	3.08 (1.26, 7.55) $P = 0.01$[1]	2.38 (0.83, 6.83) $P = 0.11$	0.93 (0.12, 7.46) $P = 0.94$	NC

NC: No convergence due to small numbers. By multivariate analysis adjusting for age at recruitment, body mass index, smoking, physical activity and alcohol use, co-morbidities (diabetes mellitus, hypertension, hypercholesterolaemia) shows: [1]P 0.05 – 0.01; [2]$P < 0.01$.

ovaries (for benign pathology) before the expected menopausal age (45-55 years). They were treated by an oestrogen-only regimen; treatment was started usually after the surgery, 17 of them were aged 20-39 years, and the other 13 women were aged less than 45 years. At that period 2000-2002, only oral oestrogen only regimen was available.

Ever-use, timing of initiation of treatment and type of regimen

As shown in Table 2, there was no significant increase in risk estimate for coronary artery disease, stroke and breast cancer in ever-users, compared with never-users. However, in ever-users, the overall risk of peripheral artery disease was significantly increased by two-fold (RR = 2.15; 0.99, 4.71; $P = 0.05$). This association was confirmed after adjusting for age, body mass index, alcohol use, physical activity, smoking and co-morbidities.

Whilst "early start" of MHT was not significantly increased for all four outcomes, "late start" was associated with a significant risk increase for coronary artery disease by 2½-fold (RR = 2.57; 1.15, 5.72; $P = 0.02$) and for peripheral artery disease by more than 4-fold (RR = 4.42; 1.55, 12.64; $P = 0.005$). A "late start" was confirmed after adjusting for other factors to be an adverse independent factor for coronary artery disease and peripheral artery disease.

Essentially, MHT was given as an oestrogen-only regimen (oral or transdermal) or oestrogen plus progestogen continuous regimen (oral or transdermal). For the oestrogen-only regimen, the risk was only significantly increased for peripheral artery disease by 5-fold (RR = 5.01; 1.62, 15.48; $P = 0.005$). The combined oestrogen plus progestogen regimen did not have an effect on any outcome. When the type of regimen was paired with the timing of initiating treatment, the risk for coronary artery disease was significantly increased by three-fold with "late start" together with the combination treatment (RR = 3.08; 1.26, 7.55; $P = 0.01$), and the risk for peripheral artery disease was significantly increased by 16-fold with "late start" together with the oestrogen-only regimen (RR = 16.73; 4.12, 67.91; $P < 0.001$). The significant independent adverse association between "late start" plus oestrogen + progestogen combination and coronary artery disease was confirmed by multivariate analysis, as was the association between "late start" plus oestrogen-only regimen and peripheral artery disease.

There were no other significant effects of MHT on other outcomes. Notably, the risk for breast cancer was not significantly affected by any variation in use.

Age of patient at start and stopping of MHT and duration of use

As shown in Table 3, there was no significant effect of age when treatment was started on risk of the outcomes until the late age group of 60-79 years (35 women in the cohort). For these women, the risk for coronary artery disease and peripheral artery disease was significantly increased (RR = 7.70; 2.85, 20.76; $P < 0.001$, and RR = 5.01; 1.27, 19.80; $P = 0.02$, respectively). The age when treatment was stopped had a similar effect on these two outcomes, when the risk was significantly increased in women aged 60-79 years.

There was a wide range of duration of use - from less than one year (but more than six months to be included) to 21-25 years (11 women) and more than 25 years (seven women, one woman used MHT for a record 31 years). There was no significant impact of duration of use on the outcomes, except for peripheral artery disease where the risk was significantly increased when use continued for 21-25 years (RR = 5.57; 1.07, 28.92; $P = 0.04$) and for more than 25 years (RR = 10.03; 1.75, 57.58; $P = 0.01$).

Notably, duration of use had no effect on risk of

Table 3 Variation of use of menopausal hormone treatment and risk of serious outcomes : Age of patient and duration of use

	Relative risk estimate (95%CI)			
	Coronary artery disease	Stroke	Peripheral artery disease	Breast cancer
Age of patient when treatment started (yr)				
20-39	0.48	0.68	1.57	0.83
	(0.07, 3.35)	(0.09, 5.35)	(0.19, 12.79)	(0.11, 6.57)
	P = 0.47	*P* = 0.72	*P* = 0.67	*P* = 0.87
40-49	1.14	0.98	2.25	0.66
	(0.55, 2.37)	(0.41, 2.37)	(0.85, 5.96)	(0.22, 1.97)
	P = 0.72	*P* = 0.97	*P* = 0.10	*P* = 0.45
50-59	0.83	1.18	1.63	0.87
	(0.37, 1.87)	(0.51, 2.75)	(0.55, 4.79)	(0.32, 2.38)
	P = 0.65	*P* = 0.69	*P* = 0.37	*P* = 0.78
60-79	7.7	2.19	5.01	1.67
	(2.85, 20.76)	(0.59, 8.11)	(1.27, 19.80)	(0.36, 7.77)
	P < 0.001	*P* = 0.24	*P* = 0.02	*P* = 0.52
Age of patient when treatment stopped (yr)				
20-39	1.36	1.22	2.79	1.48
	(0.38, 4.88)	(0.27, 5.56)	(0.57, 13.53)	(0.32, 6.85)
	P = 0.64	*P* = 0.80	*P* = 0.20	*P* = 0.61
40-49	0.48	0.54	0.92	0.32
	(0.18, 1.27)	(0.18, 1.59)	(0.25, 3.37)	(0.97, 1.41)
	P = 0.50	*P* = 0.26	*P* = 0.90	*P* = 0.13
50-59	1.3	1.24	2.83	1.75
	(0.61, 2.80)	(0.51, 3.00)	(1.06, 7.60)	(0.74, 4.16)
	P = 0.50	*P* = 0.64	*P* = 0.04	*P* = 0.20
60-79	4.98	2.99	4.18	NC
	(2.19, 11.55)	(1.11, 8.08)	(1.24, 14.14)	
	P < 0.001	*P* = 0.03	*P* = 0.02	
Duration of use (yr)				
< 1	1.1	NC	3.59	1.91
	(0.24, 5.04)		(0.72, 17.75)	(0.40, 8.98)
	P = 0.90		*P* = 0.12	*P* = 0.41
1-5	0.76	1.28	1.18	0.85
	(0.31, 1.87)	(0.53, 3.11)	(0.32, 4.34)	(0.28, 2.57)
	P = 0.55	*P* = 0.59	*P* = 0.81	*P* = 0.77
6-10	2.12	0.3	1.43	0.37
	(0.90, 5.03)	(0.04, 2.32)	(0.31, 6.74)	(0.40, 2.85)
	P = 0.09	*P* = 0.25	*P* = 0.65	*P* = 0.34
11-15	0.75	1.69	3.14	0.95
	(0.26, 2.20)	(0.65, 4.38)	(1.04, 9.50)	(0.27, 3.35)
	P = 0.60	*P* = 0.28	*P* = 0.04	*P* = 0.94
16-20	2.75	1.29	NC	0.74
	(0.93, 8.11)	(0.28, 5.92)		(0.09, 5.84)
	P = 0.07	*P* = 0.74		*P* = 0.78
21-25	2.89	2.44	5.57	1.33
	(0.73, 11.41)	(0.50, 11.92)	(1.07, 28.92)	(0.16, 10.96)
	P = 0.13	*P* = 0.27	*P* = 0.04	*P* = 0.79
26+	1.28	1.83	10.03	NC
	(0.15, 10.97)	(0.21, 15.80)	(1.75, 57.58)	
	P = 0.82	*P* = 0.58	*P* = 0.01	

NC: No convergence due to small numbers.

coronary artery disease, stroke and breast cancer.

DISCUSSION

When our LAW study was planned some 14 years ago, it was considered an opportunity to test the effects of the variables in the use of MHT because there was a suitable group of women aged 40-79 years at recruitment who were randomly invited from the population to join the study. The findings of WHI study gave an impetus to investigate the impact of variation in use such as early and late initiation of treatment and type of hormone regimen on relative risks of major clinical outcomes. For this report, we chose arterial conditions in the heart, brain and periphery (carotid, femoral, popliteal arteries). We included peripheral artery disease because of its association with older women and there were 29 events in our study. This study differed from other large studies in several aspects: the women were given MHT by their individual medical practitioners because of clinical indications, not to asymptomatic volunteers; the study was longitudinal and non-interventional, not randomised placebo-controlled; the cohort was smaller but closely followed for 14 years with very good outcome information on all the women; and despite the smaller cohort size, there were adequate outcome events to allow the power for analysis, based on relative risks estimated by comparison with an adequate group of never-ever users, as reference.

The present study confirms the general view that MHT is generally safe in healthy women. However, it may have unfavourable effects on the vascular system, both arterial and venous. In particular, risks of cardio-vascular disease have been extensively analysed - with differing results between cohort, retrospective and prospective observational studies and randomised controlled studies. Whereas the observational studies (liable to inherent bias such as the "healthy user effect") demonstrated a significant 40%-60% reduction in risk of disease and of mortality[10-12], the controlled studies (susceptible to faulty matching, loss to follow-up) showed no significant decrease, or even an increase as found by the WHI study with a risk increase with the oestrogen plus progestogen regimen[2] and a decrease with the oestrogen-only regimen[1]. We found in our prospective and observational study a significant increase in risk of clinically-reported coronary artery disease only with "late start" to initiate treatment more than three years from onset of menopause, and when treatment was started when the woman was much older, aged 60-79 years. This age-group is certainly considered contra-indicated now to start MHT but some of these women had been treated more than 20-30 years ago, based on a different set of evidence. Notably, ever-use of MHT generally had no significant effect on coronary artery disease, a common health outcome in ageing. We believe the increased risk associated with "late start" reflected old practice when MHT was considered safe and beneficial to the heart; since WHI, the older and less healthy women were advised to stop MHT by their medical practitioner. Therefore, our findings on risk of coronary artery disease support use in women within three years from menopause and started before age 60 years; duration of use did not appear to have a significant impact on the disease.

Risk of stroke with MHT was variably estimated by many studies, with the view that risk was increased with ischaemic stroke but not with haemorrhagic stroke[13,14]. Although the risks were increased in WHI studies (RR =

1.31; 1.02, 1.68 ischaemic stroke), they were not found in the post intervention phase of the study[15-16]. There appears to be general agreement that the risks for all types of stroke were increased, as in total stroke, non-fatal but stroke leading to disability; and no significant heterogeneity with any subgroups[17]. However, an association with oestrogen dose has been reported[18], but not with age or time since menopause, or with low dose transdermal patch. We found no effect of MHT on risk of stroke, regardless of current or past use, timing of initiation of treatment from menopause or hormone content in the 42 events recorded in our cohort. The younger user effect may explain the finding, or more follow-up time is required to show this effect in light of the increasing incidence of hypertension with time in the cohort.

There is one vascular outcome seldom analysed with MHT - that is, the effect on peripheral artery disease. Because the disease is a component of the spectrum of arterial diseases, we decided to investigate its risk as a clinical condition which is less studied in epidemiological studies because it occurs less frequently - 29 events in our cohort of 489 women. We included clinically-proven diseases in the carotid, femoral and popliteal systems. As shown in the results, MHT had a strong impact on the risk of peripheral artery disease during follow-up of 14 years. The risk was significantly increased with "ever-use" and "late start", oestrogen-only regimen, and older age of women when treatment was started or stopped, and confirmed as a significant adverse association by multivariate analysis after adjusting for lifestyle factors and co-morbities. This is the only outcome where duration of use had a significant impact; from a duration of 11 years onward, the risk was significantly increased. We believe that the effect relates more to older women who already have existing atherosclerosis of the peripheral arteries.

Breast cancer was the cancer outcome selected for analysis because of its frequency of occurrence and the known influence of hormones on the breast. Consideration has been given to contributing factors such as type of MHT, duration of use, body mass, interval between menopause and initiation of therapy, previous MHT, mammographic density[5]. Generally, the studies suggest an increase in risk. The Collaborative Group found the risk of breast cancer increased by 2.3% (RR = 1.023; 1.011, 1.036) per year of use, reaching 35% (RR = 1.35; 1.21, 1.49) after five years[19]. The Million Women Study also found an increased risk for oestrogen plus progestogen regimen by 100% (RR = 2.00; 1.88, 2.13) and less with oestrogen-only regimen by 30% (RR = 1.30; 1.21, 1.45), with no differences between routes of administration[3]. Also, an increased risk of breast cancer was found with increasing body weight - with a 3.1% increase per kg/m^2 of body mass index[20]. However, the increased risk was significantly greater in thin women using MHT, than overweight and obese women. The importance of timing of initiation of MHT from onset of menopause, the so-called "gap time" or defined in our study as "early start" and "late start" has been highlighted in more recent studies. The WHI and MWS studies found an increased risk when the cut-off was 10 years after menopause, with the risks greater when MHT was given late (RR = 2.04 *vs* 1.53) for oestrogen plus progestogen regimens. For oestrogen-only regimens, the risk estimate fell from 1.43 to an insignificant 1.05. The reasoning behind these findings is based on the premise that exogenous hormones accelerate growth of pre-existing occult breast cancer (mitogenic and not carcinogenic) and differential sensitivity of breast tissue to hormones is related to age and menopausal status. We found no significant effect of MHT on risk of breast cancer, regardless of the use variation analysed. It is possible the small number of events (32 events) of breast cancer in our study, did not allow an appropriate calculation of risk estimate in the cohort. However, it is reassuring that there was no apparent significant risk increase.

In conclusion, the study found the use of MHT was associated with no overall increased risk of coronary artery disease, stroke and breast cancer, and an increased risk of peripheral artery disease. However, variation in use may have an adverse impact on some outcomes, for example, when MHT was started long after onset of menopause in much older women over the age of 60 years, there was a significant increase in risk for coronary artery disease and peripheral artery disease.

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COMMENTS

Background

The study examined the effects of hormones (estrogen and progestogen) given in different ways on long-term serious outcomes in post-menopausal women. This field of clinical remains controversial because of mixed reports.

Research frontiers

The area of women's health continues to be argued about whether hormone treatment is beneficial or harmful.

Peer-review

The availability of long-term use data is consistent with previous experience and might have been more directly related to the women on ET for post-oophorectomy life.

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