

Relation between cigarette smoking and use of hormonal replacement therapy for menopausal symptoms

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SUMMARY The aim of this study was to characterise new users of hormonal replacement therapy (HRT) for the relief of menopausal symptoms and to compare these women with never-users of HRT; 402 new users and 804 never-users were studied. Hot flushes were the most common symptom in both users and non-users and were the most frequent reason for prescribing HRT. The prevalence of menopausal symptoms in non-users of HRT was high although substantially lower than that in users. HRT users were more likely to be current cigarette smokers than were never-users. There was also, within smokers, a significant relation between the number of cigarettes smoked and the likelihood of using HRT. This relation between HRT use and smoking could result from an anti-oestrogen effect of smoking, intensifying menopausal symptoms. Of potential clinical relevance is the suggestion that a proportion of women using HRT may be doing so in order to alleviate smoking-induced symptoms. Users of HRT were also more likely to have used oral contraceptives than were never-users; this relation was probably behavioural.

Several epidemiological studies have assessed the relation between HRT use and the risks of death, coronary heart disease, or stroke. In some, the effect of HRT has been assessed as protective,^{1 2} in another³ as a risk factor, and in others⁴⁻⁷ HRT has appeared to have no effect. Most of this published work is based on studies of women in the USA. An investigation of the relation between HRT use and the subsequent development of stroke or myocardial infarction based on United Kingdom data and relevant to the current picture of HRT prescribing in general practice is therefore of obvious interest, and a case-control study is in progress in this unit. The study comparing HRT users with never-users presented here was designed to provide information about possible confounding factors. An unexpected finding of the study is the indirect suggestion that many women using HRT may be doing so in order to alleviate smoking-induced symptoms.

Methods

PARTICIPANTS

The study was based in general practices belonging to

the Medical Research Council's General Practice Research Framework.⁸ During the period September 1982 to January 1984, all women aged 45–69 on the lists of these practices who were prescribed HRT for the first time became "case" patients, unless their notes were incomplete or the HRT was prescribed for some reason other than the relief of menopausal symptoms. For each patient, two controls who had never used HRT were selected by searching in sequence through the age/sex register of the same general practitioner. The controls were matched for age, within two years, and for ethnic group. The first two people to satisfy the matching criteria were always selected. If a person selected was unwilling or unavailable to act as control, the next eligible person on the register was then asked. Details of smoking history, oral contraceptive use, marital status, reproductive history, and menopausal status and symptoms were obtained at interview. Because of the difficulty of obtaining an objective assessment in this study, no attempt was made to grade the severity of menopausal symptoms; these were classified only as present or absent. The planned study size, 350 cases, was chosen to permit the demonstration of a true difference between users and controls of 10% in, for instance, the proportions who were smokers, significant at the 5% level with at least 85% power.

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STATISTICAL TECHNIQUES

The analysis involved conditional maximum likelihood logistic regression⁹ using an adaptation of a published computer program.¹⁰ The estimates of odds ratios thus obtained refer to the relative chance of members of two contrasted groups, for example, smokers and non-smokers, becoming HRT users. Possible risk variables were considered both singly and jointly, using a forward stepwise selection procedure. The p-values presented are exact down to 0.001, below which p < 0.001 is quoted.

A very few unknowns in the menopausal history details (less than 1% of answers) were considered as negative histories, except for questions on loss of libido and dyspareunia where the more extensive number of unknowns formed a separate category.

Results

Altogether 402 users, each matched with two controls, were recruited. Of those first approached 23% refused or were not available to act as controls, and the next eligible person on the age/sex register was invited as a substitute.

Marital status, parity, and menopausal status did not differ significantly between users and controls (table 1). Users were more likely to be ever-users of oral contraceptives (odds ratio = 1.48, p = 0.004).

The reported prevalence of menopausal symptoms was greater in users than in controls (table 2) but was substantial even in controls. Two or more of the six most common symptoms (hot flushes, night sweats, irritability, depression, insomnia, impaired memory or concentration) were commonly present together in one patient. Hot flushes was both the commonest

Table 2 History of menopausal symptoms reported at interview*

Symptom	% Users	% Controls
Hot flushes	82.3	52.2
Night sweats	76.1	40.8
Irritability	63.7	41.0
Depression	60.0	32.6
Insomnia	55.2	30.1
Impaired memory/concentration	54.5	36.1
Loss of libido: yes	36.6	24.6
unknown	8.2	7.7
Dyspareunia: yes	18.7	10.8
unknown	8.2	8.3

*p value for all user-control comparisons < 0.001

symptom reported (table 2) and the commonest reason for prescribing HRT.

Users were more likely to be current smokers than were controls (odds ratio = 1.46, p = 0.005) (tables 1 and 3 (a)), and to smoke more than controls (table 3 (b)). Within smokers, there was a strong relation between HRT use and the number of cigarettes smoked (p = 0.009). There was no relation between ex-smoking and HRT use. Multiple regression analysis showed that the two associations, between HRT use and current smoking, and between HRT and oral contraceptive use, were independent of one another. The prevalence of menopausal symptoms in smokers was greater than that in non-smokers (table 4). Stepwise multiple regression analysis using number of cigarettes currently smoked and

Table 1 Characteristics of participants

	Users N = 402	Controls N = 804
Mean age (SD) years	50.5 (3.9)	50.5 (4.0)
% Married	83.8	83.4
% Parous	87.1	86.0
% Still menstruating	43.8	47.9
% Cigarette smokers	34.1	26.4
		p = 0.005*
		OR 1.46
		95% CI 1.11-1.91
% Ex-cigarette smokers	20.1	21.5
% Ever-use of oral contraceptive	39.1	31.1
		p = 0.004*
		OR 1.48
		95% CI 1.13-1.94

*p value for comparison of prevalence in users with that in controls OR. Relative risk compares prevalence in users with that in controls. 95% CI = 95% confidence intervals around OR.

Table 3 (a) Users and controls: distribution according to smoking habit

	Users		Controls	
	N	%	N	%
Smokers				
Never	184	45.8	419	52.1
Ex	81	20.1	173	21.5
Current	137	34.1	212	26.4
Total	402	100.0	804	100.0

(b) Users and controls: distribution of current smokers according to number of cigarettes smoked

Cigarettes/day	Users		Controls	
	N	%	N	%
1-10	42	31	98	46
11-20	78	57	100	47
>20	17	12	14	7
Total	137	100	212	100

Table 4 Prevalence of some menopausal symptoms by current cigarette smoking habit (number and percentage)

	Current smokers N = 349		Ex- or never-smokers N = 857	
	No.	%	No.	%
Hot flushes	241	69	509	59
Night sweats	207	59	427	50
Irritability	199	57	387	45
Depression	175	50	328	38
Insomnia	156	45	308	36

menopausal symptoms as independent variables suggested that the association between current smoking and HRT use was secondary to and therefore possibly mediated through the relation between menopausal symptoms and HRT use. Thus, once menopausal symptoms had been taken into account, the inclusion of the number of cigarettes smoked made no significant further contribution ($p=0.11$) to the likelihood of HRT use.

Discussion

A relation shown in these data between the use of oral contraceptives and HRT is likely to be behavioural: use of oral contraceptives was not related to the prevalence of menopausal symptoms, and the length of time elapsing since oral contraceptive use was similar in users and non-users of HRT. Possibly women who use oral contraceptives during their reproductive years may also tend to ask their doctors to prescribe HRT when they become menopausal.

The relation between smoking and HRT use shown here can be explained by a greater prevalence of menopausal symptoms in smokers than in non-smokers. This, together with the significant dose-response relation between the stated number of cigarettes smoked at the time and HRT use, and the fact that ex-smoking was not associated with HRT use, suggests that smoking may initiate or aggravate the symptoms for which HRT is prescribed, possibly through an "anti-oestrogenic" extra-ovarian effect.¹¹ This effect could be direct, by inducing microsomal oxidative systems, or by altering oestrogen binding. Increased degradation of exogenous oestrogens in smokers compared with non-smokers has been suggested.¹² It could be indirect: circulating androgens are in part converted to oestrogens by fat,^{13 14} and smokers tend to be leaner than non-smokers. In this sense, any weight differences would be another part of the postulated chain linking smoking and menopausal symptoms. It is possible that cigarette smoking is a result, not a cause, of menopausal symptoms, but this seems a less likely explanation, since smoking habit would have had to be very strongly affected to produce

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a dose-response relation. Both explanations may apply. It is also possible that there may be a group of women predisposed by some unidentified factor (for example, behavioural characteristics) to both smoking and the use of HRT. Here, too, the relation would need to be very strong to result in a dose-response effect. Doctors may be more ready to prescribe HRT for smokers than for non-smokers in an attempt to reduce smoking-associated osteoporosis,^{12 15-17} but it is unlikely that this consideration affected prescribing practice. It seems more probable that a proportion of women using HRT are doing so in order to alleviate smoking-induced symptoms.

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