Duration of Estrogen Replacement Therapy in Relation to the Risk of Incident Myocardial Infarction in Postmenopausal Women

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Background: There is little information about whether an increasing duration of estrogen replacement therapy is associated with a declining risk for myocardial infarction in postmenopausal women.

Objective: To conduct a population-based, case-control study among enrollees of the Group Health Cooperative (GHC) of Puget Sound, Seattle, Wash.

Subjects and Methods: Case subjects were all postmenopausal women who were enrolled in the GHC with an incident fatal or nonfatal myocardial infarction from July 1985 through December 1993. Control subjects were a stratified random sample of postmenopausal women who were enrolled in the GHC without myocardial infarction and matched to case subjects by age and calendar year. We reviewed the medical records of the 850 case subjects and 1974 control subjects and conducted telephone interviews with consenting survivors. Use of estrogen or estrogen and progestin was assessed using GHC's computerized pharmacy database.

Results: Among women who were currently using estrogen, a longer duration of use was inversely associated with a risk for myocardial infarction after adjustment for age, year of identification, diabetes mellitus, angina, and smoking. For categories of increasing duration of estrogen use (never, >0-<1.8 years, 1.8-<4.2 years, 4.2-<8.2 years, and ≥8.2 years), the odds ratios for myocardial infarction were 1.00 (reference), 0.91, 0.70, 0.65, and 0.55 (for trend among the current users, $P=.05$). Among women who had used estrogen in the past, there was no evidence of decreasing risk with increasing duration of estrogen use.

Conclusion: In this study, a long duration of hormone replacement therapy among women currently using estrogen was associated with a reduced risk for first myocardial infarction.

Arch Intern Med. 1997;157:1330-1336

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THE RESULTS of observational studies[1] suggest that estrogen replacement therapy in women after menopause is associated with a decreased risk for first coronary heart disease (CHD) events; the summary relative risk for women who have ever used estrogen compared with those who have never used estrogen from a meta-analysis by Stampfer and Colditz[2] was 0.56 (95% confidence interval [CI], 0.50-0.61). However, to our knowledge, there is little information about whether the risk continues to decline in association with increasing duration of therapy. Estrogen has many effects that may assume varying degrees of importance during short-term as opposed to long-term therapy. Mechanisms that may be important during short-term use of estrogen include its procoagulant activity, particularly at high doses,[3] and its effects on the functions of the endothelium and vascular smooth muscle.[4] The favorable effect of estrogen on the lipid profile,[3] decreased formation of new plaques, and stabilization of existing plaques[4] may be more important during long-term use. The relative importance of these mechanisms may also depend on underlying atherosclerosis, smoking habits, or other risk factors of CHD.

We conducted a population-based, case-control study of hormone replacement therapy in relation to a risk of cardiovascular disease in women. An earlier report examined the risk for incident fatal or nonfatal myocardial infarction (MI) in association with the current use of combined estrogen and progestin therapy.[5] Additional case subjects and control subjects who were added since that report provided an opportunity to examine the relationship between duration and recency of estrogen use and a risk for MI.

SUBJECTS AND METHODS

SETTING

The setting for this project was the Group Health Cooperative (GHC) of Puget Sound, Seattle, Wash, a staff-model health maintenance organization. The project was approved by the institutional review boards of the University of Washington, Seattle, and GHC. Recommendations regarding the use of estrogen replacement therapy in postmenopausal women were circulated to the primary care medical staff of GHC in 1985 by the GHC Committee on Osteoporosis and in 1987 and 1988 by the GHC Department of Obstetrics and Gynecology.

IDENTIFICATION OF SUBJECTS

Case subjects were all postmenopause, aged 30 to 79 years, who were enrolled in the GHC and diagnosed as having an incident fatal or nonfatal MI from July 1986 through December 1993. Control subjects were a stratified random sample of postmenopausal women who were enrolled in the GHC. We identified potential subjects from the following: (1) the computerized discharge abstracts for the 2 GHC hospitals; (2) the bills for services provided by non-GHC physicians and health care facilities; and (3) the results of a computerized match between the GHC enrollment files and the death registry files of the state of Washington. Research assistants were trained to identify events that were clearly not MIs and events that were clearly MIs. Borderline or questionable events were reviewed by physicians without knowledge of the subjects' use of hormone replacement therapy. We have used these methods in previous studies.[5-7] In a blinded validation study,[5] the completeness of case ascertainment was 95%, and 97% of eligible case subjects met standard criteria for definite or probable MI.

Control subjects were frequency matched to the case subjects by age (within decade) and calendar year at a ratio of 2:1. Control subjects met the same eligibility criteria as the case subjects but had not had an MI.

INDEX DATES AND ELIGIBILITY

Each patient was assigned an index date. For the case subjects, the index date was the date of admission for the first acute MI or the date of death for those with fatal MIs out of the hospital. For the control subjects, the index date a computer-generated random date within the same year for which they had been sampled as control subjects. For all subjects, we collected information about risk factor status only before the index date. We excluded the following: (1) subjects who were enrolled for less than 1 year or had fewer than 4 visits before their index dates; (2) those who were not postmenopausal; (3) those who had previously had an MI; or (4) those whose MI was a complication of a procedure or surgery. Menopause was defined as the cessation of ovarian function due to either natural menopause or bilateral oophorectomy before natural menopause. A notation in the medical record of the cessation of menses or, in women who had undergone a hysterectomy, the symptoms of the menopause was used to establish the date of menopause. Women aged 55 years or older for whom menopausal status at the index date was not clear from the medical record were assumed to be postmenopausal. Women younger than 55 years whose menopausal status at the index date could not be determined were excluded; only 10 (0.3%) of otherwise eligible women were excluded for this reason.

DATA COLLECTION AND DEFINITION OF DURATION OF HORMONE USE

Data collection included a review of the GHC ambulatory medical record and a telephone interview of consenting survivors. Trained research assistants reviewed the medical record to determine eligibility and collect information about risk factors for CHD, such as smoking status, weight, hysterectomy status, use of health services, marital status, and preexisting medical conditions, such as hypertension, angina, diabetes mellitus, congestive heart failure, stroke, and peripheral vascular disease. Angina was defined as probable or definite angina based on the notes of the primary care physician and consultants and the results of diagnostic tests. Hypertension was defined as pharmacologically treated hypertension; and diabetes mellitus, disease treated pharmacologically with oral hypoglycemic medication and/or insulin. The telephone interview sought information about risk factors, such as smoking status, physical activity, education, and race. The median interval between the index date and the telephone interview was 24 months. Myocardial infarction events were validated by a review of available inpatient medical records.

The GHC computerized pharmacy database was used to assess hormone use. Since 1976, the GHC pharmacy database has included a record for all prescriptions dispensed to GHC enrollees. Each pharmacy record includes a patient identifier, the drug type and dose, the date

Continued on next page

RESULTS

There were 905 postmenopausal women, aged 30 to 79 years, who were diagnosed as having an incident fatal or nonfatal MI from July 1986 through December 1993; 850 (93.9%) participated in this study and had complete data. Of these 850 women, 67 (7.9%) died out of a hospital; 89 (10.5%) died in a hospital; and another 694 (81.6%) sustained nonfatal MIs. We identified 2093 eligible control subjects from the membership of GHC; 1974 (94.3%) participated and had complete data. Only 49 (2%) of the subjects were younger than 50 years at the index date.

The average duration of enrollment in GHC before the index date was 17 years. As expected, MI case subjects had higher levels of total cholesterol and lower levels of high density lipoprotein (HDL) cholesterol than control subjects; a larger proportion of MI case subjects than control subjects had a history of angina, hypertension, or diabetes mellitus and were currently smoking at the index date (**Table 1**).

Although many health care plans at GHC include small to moderate copayments for drugs, the use of GHC pharmacies was extremely high among GHC enrollees. Data from the telephone interview indicated that 346 (95.1%) of the

dispensed, the quantity dispensed, and dosing instructions. Since information on hormone use obtained from the telephone interview was not available on all subjects and since subjects were often unable to recall the duration of therapy, information on duration of hormone use was restricted to that obtained using pharmacy data.

We defined subjects who had ever used estrogen as those with a record of filling at least 2 prescriptions; current use of estrogen included subjects who had received a quantity of pills sufficient to last until the index date. To determine current use, we searched the pharmacy data for the hormone prescription immediately preceding the reference date. The number of days that a prescription would last was calculated as follows:

[Number of Pills Dispensed / (Pills per Day Prescribed × Assumed Compliance Rate)] × [(Days in a Month)/ (Days per Month That the Hormone Was to Be Taken)]

If a woman (who was 80% compliant) received enough pills to last until her index date, we considered her a current user.

For determining the duration of use, we used the dosing instructions to calculate the number of days that each prescription would last if the woman was 80% compliant. If a subsequent prescription was filled before a particular prescription was calculated to run out, we assumed that the pills remaining from the first prescription were not taken. The duration of estrogen use included the duration of both unopposed estrogen and estrogen used in combination with a progestin. To determine the duration of progestin use, we included only progestins used in combination with estrogen; exposure to unopposed progestins was not included. The total number of months each subject was exposed to estrogen and progestin was calculated by summing the duration of exposure recorded in the GHC pharmacy database since 1976. Analyses using measures that assumed 100% compliance rather than 80% compliance produced similar results, so we present only the data from the pharmacy-based measures that assumed 80% compliance.

Based on the review by Lobo,[8] we assumed that the following doses of different formulations of estrogen were equivalent: 0.625 mg of conjugated estrogen, 0.625 mg of esterified estrogen, 1 mg of piperazine estrone sulfate, 1 mg of micronized estradiol, 1 mg of estradiol valerate, and 0.005 mg of ethinyl estradiol.

ANALYSES

Data were complete for the variables defining duration of hormone use, and information on medical conditions, such as angina, diabetes mellitus, and hypertension, was uniformly available from the review of the medical record. Information on smoking status at the index date was missing for 60 (2.1%) of the otherwise eligible subjects; subjects with missing data for smoking were excluded.

In preliminary analyses, we considered information on several risk factors for CHD obtained from the review of the medical record and the telephone interview. Data from the review of the medical records were missing for fewer than 36 (2%) of the subjects for the following continuous variables: height, weight, number of physician visits in the year before the index date, time elapsed since undergoing a hysterectomy, and time enrolled in GHC. In the preliminary analyses, we imputed the case or control mean for each woman with an unknown value for these variables. For categorical variables, the agreement between medical record and self-reported measures was good to excellent (κ=0.83 to κ=0.88) for race (black vs other), current smoking (yes or no), hysterectomy (yes or no), and education (κ=0.69) (less education than a high school graduate vs high school graduate or higher level of education). Self-reported data, if available, were used for these variables; if not, then covariate data from the medical record were used. For these combined categorical variables, data were missing on race (208 [7.2%]), hysterectomy status (120 [4.2%]), marital status (99 [3.4%]), and physical activity (349 [12.1%]). The confounding effects of these continuous and categorical covariates were small or absent whether imputed values were used for subjects with unknown values or complete case analysis was done. None of these covariates were included in the final multivariate models presented here.

For subjects who had used estrogen, quartiles of the duration of estrogen use were calculated based on the distribution of the duration of use in the control subjects who were currently using estrogen. For analyses of a risk for MI in relation to time since discontinuation of estrogen use, 4 categories of time since discontinuation were constructed, based on quartiles of the distribution in the control subjects who had used estrogen in the past.

We used logistic regression analysis[9] to obtain maximum likelihood estimates of odds ratios (ORs) for categories of increasing duration of estrogen use, adjusted for multiple potential confounding factors. The logistic regression analyses were conducted using the complete case method.[10] All statistical tests were 2-tailed. All tests for linear trend were conducted using the lowest quartile of duration of use as the reference group.[11]

case subjects and 1073 (94.5%) of the control subjects interviewed filled all their prescriptions at a GHC pharmacy, and 351 (96.4%) of the case subjects and 1099 (96.7%) of the control subjects interviewed received all or almost all their drugs (90%-100%) from a GHC pharmacy.

Estrogen replacement therapy (either unopposed or in combination with a progestin) had been used at any time by 229 (27%) of the case subjects with MI and 700 (35%) of the control subjects; the average duration of use was 3.9 years for case subjects and 4.0 years for control subjects (**Table 2**). Progestin in combination with an estrogen had been used at any time by 87 (10%) of the case subjects with MI and 267 (14%) of the control subjects; the average duration of combined therapy was 2.5 years for case subjects and 2.2 years for control subjects. Combined continuous therapy with both an estrogen and a progestin taken daily was not used at the index date by any subjects with index dates before 1989. Among women taking both estrogen and progestin at the index date, combined continuous therapy was used by less than 11% of case subjects and control subjects with index dates in 1989 through 1991, by 6 (27%) of both the case subjects and control subjects with index dates in 1992, and by 5 (42%) of the case subjects and 14 (47%) of the control subjects with index dates in 1993.

Among control subjects who had used estrogen, increasing age, increasing duration of GHC enrollment, and having undergone a hysterectomy were associated with increasing duration of estrogen use (**Table 3**).

Overall, the use of estrogens at any time was associated with a 28% decrease in the risk of MI compared with never using estrogens (**Table 4**) (OR, 0.72; 95% CI, 0.59-0.88); current use was associated with a 30% decrease in risk (OR, 0.70; 95% CI, 0.55-0.89); and past use was associated with a 26% decrease in risk (OR, 0.74; 95% CI, 0.57-0.96). Although women who were currently using estrogen had an overall risk for MI that was slightly lower than that of women who had used estrogen in the past (OR, 0.70 vs OR, 0.74), after additional adjustment for duration of use in analyses restricted to subjects who had ever used estrogen, this advantage was completely eliminated.

A risk for incident MI associated with the duration of use was examined separately in subjects who had ever used, were currently using, and had previously used estrogen (**Table 5**). Among those who had ever used estrogen, a longer duration of use was associated with a suggestion of decreased risk, but this trend was not statistically significant. Additional adjustment for recency of use (past vs current use) in analyses restricted to the subjects who had ever used estrogen did not change the results at all.

For women who were currently using estrogen, a longer duration of use was inversely associated with a risk for MI after adjustment for age, year of identification, diabetes mellitus, angina, and smoking (*P* for trend, .05). Further adjustment for time in GHC, time since hysterectomy, physician visits in the last year, hypertension, stroke, peripheral vascular disease, congestive heart failure, use of progestins, family history of CHD, hysterectomy status, physical activity, height, weight, race, and marital status had little effect on the estimated ORs. Among the women who were currently using estrogen, the risk for nonfatal MI according to duration of estrogen use (adjusted ORs, 1.00 [reference, subjects who had never used estrogen], 1.02, 0.79, 0.63, and 0.61) was similar to that for fatal and nonfatal MIs combined. The risk for MI among women who used unopposed estrogen at the index date, according to the duration of use, was similar to that among users of unopposed or estrogen and progestin therapy at the index date (adjusted ORs, 1.00 [reference, subjects who had never used estrogen], 0.90, 0.75, 0.62, and 0.55). The number of women with fatal events and the number using estrogen and progestin therapy were too small to examine separately. In analyses restricted to subjects who were currently using and those who had

Table . Characteristics of Case Subjects With Myocardial Infarction and Control Subjects*

Variable	Case Subjects (n=850)	Control Subjects (n=1974)
Age, y	68.7	68.5
Time in GHC, y	17.0	17.1
No. of physician visits in last year	8.1	6.3†
Cholesterol, mmol/L (mg/dL)	6.64 (256.9)	6.19 (239.4)†
HDL cholesterol, mmol/L (mg/dL)	1.32 (51.2)	1.52 (58.6)†
Angina, %	21.4	6.3†
Hypertension, %	52.4	35.1†
Diabetes mellitus, %	21.2	5.3†
Current smoker, %	32.5	16.3†
Hysterectomy, %	37.5	40.3
Married, %	52.3	59.9†

*GHC indicates the Group Health Cooperative of Puget Sound, Seattle, Wash; HDL, high density lipoprotein. Proportion of subjects with missing data for each variable is included in "Subjects and Methods" section; total cholesterol levels were available for 84.5% of case subjects and 87.2% of control subjects; HDL cholesterol levels were available for 58.7% of case subjects and 57.9% of control subjects.

†$P<.001$ for comparison of case subjects and control subjects.

Table . Pharmacy-Based Measures of Estrogen and Progestin Use*

Variable	Estrogen Use		Combined Estrogen and Progestin Use	
	Case Subjects (n=850)	Control Subjects (n=1974)	Case Subjects (n=850)	Control Subjects (n=1974)
Women who had ever used estrogen				
No. (%)	229 (27)	700 (35)	87 (10)	267 (14)
Mean (±SD) duration of use, y	3.9±3.7	4.0±3.7	2.5±2.2	2.2±2.0
Percentage of women who were current users	55.0	58.7	48.3	50.2
Women who were currently using estrogen				
No. (%)	126 (15)	411 (21)	42 (4.9)	134 (6.8)
Mean (±SD) duration of use, y	4.8±4.1	5.1±3.9	2.8±2.7	2.6±2.2
Mean (±SD) days per month				
Estrogen	26.1±2.8	26.0±2.6	26.3±2.9	26.3±2.7
Progestin			17.6±14.2	14.1±7.7
Mean (±SD) dose per day, mg				
Estrogen	0.67±0.26	0.65±0.31	0.68±0.24	0.64±0.30
Progestin			10.5±11.6	8.2±3.0
Women who had used estrogen in the past				
No. (%)	103 (12)	289 (15)	45 (5.3)	133 (6.7)
Mean (±SD) duration of use, y	2.8±2.9	2.5±2.6	2.1±1.6	1.8±1.7

*Estrogen use includes use of either unopposed estrogen or estrogen in combination with a progestin. All estrogen doses were converted to the equivalent doses of conjugated estrogen, and all progestin doses were converted to the equivalent doses of medroxyprogesterone acetate. Ellipses indicate not applicable.

Table 3. Characteristics of Control Subjects by Duration of Estrogen Replacement Therapy at the Index Date*

Variable	Control Subjects Who Had Never Used Estrogen (n=1274)	Control Subjects Who Were Currently Using Estrogen and Those Who Had Used Estrogen in the Past			
		Duration of Estrogen Use, y			
		>0-<1.8 (n=267)	1.8-<4.2 (n=171)	4.2-<8.2 (n=145)	≥8.2 (n=117)
Age, y	69.9	65.2	65.4	66.5	68.2†
Time in GHC, y	17.1	16.1	14.6	17.6	22.7†
No. of physician visits in past year	6.0	6.9	6.7	7.0	6.4
Angina, %	7.5	3.0	2.9	6.2	6.0
Hypertension, %	35.8	30.3	35.1	37.2	35.0
Diabetes mellitus, %	6.4	3.4	1.8	7.6	0.9
Current smoker, %	17.1	13.5	14.0	17.2	15.4
Hysterectomy, %	27.9	49.8	57.9	70.4	87.9†
Married, %	56.6	68.2	61.7	66.2	67.0

*GHC indicates the Group Health Cooperative of Puget Sound, Seattle, Wash. Proportion of subjects with missing data for each variable is included in "Subjects and Methods" section.
†P<.005 for comparison of control subjects with longest duration of estrogen use (≥8.2 years) with control subjects with shortest duration of estrogen use (>0-<1.8 years).

Table 4. Association of Myocardial Infarction With Estrogen Use

Estrogen Use	No. of Case Subjects	No. of Control Subjects	Odds Ratio*	95% Confidence Interval
Never	621	1274	1.00	Reference
Estrogen use	229	700	0.72	0.59-0.88
Current	126	411	0.70	0.55-0.89
Past	103	289	0.74	0.57-0.96

*The risk for myocardial infarction was adjusted for age, year of identification, diabetes mellitus, angina, and current smoking.

never used estrogen for whom HDL cholesterol levels were available (subjects currently using estrogen: 86 case subjects and 279 control subjects; those who had never used estrogen: 344 case subjects and 677 control subjects), a similar decline in risk with increasing duration of use was observed (adjusted ORs, 1.00 [reference, subjects who had never used estrogen], 0.86, 0.69, 0.75, and 0.48), but after additional adjustment for HDL cholesterol levels, the decline in the risk for MI across levels of increasing duration of use was attenuated (adjusted ORs, 1.00 [reference, subjects who had never used estrogen], 0.87, 0.77, 0.86, and 0.61).

Among the subjects who had used estrogen in the past, there was no evidence of decreasing risk with increasing duration of estrogen use; the trend seen, although not significant, was in the opposite direction. We examined the risk for MI in subjects who had used estrogen in the past according to the time since the discontinuation of estrogen use. Women who had discontinued the use of estrogen recently, within 8 months (0.7 years) of the index date, had a slightly higher risk for MI (OR, 1.43; 95% CI, 0.67-3.06) than those who discontinued estrogen use 0.7 to 2.7 years before the index date. Women who discontinued estrogen use 2.7 to 6.7 years or 6.7 years or longer before the index date had a risk for MI similar to or higher than that of subjects who had recently stopped using estrogen. Since women who had recently discontinued estrogen use appeared to be at an increased risk for MI, we reanalyzed the association between the duration of estrogen use and the risk for MI in subjects who had used estrogen in the past, after eliminating the 101 subjects who had discontinued estrogen use within 8 months of the index date. The adjusted relative risks for incident MI across levels of increasing duration of estrogen use were 1.00 (subjects who had never used estrogen), 0.76, 0.67, 0.80, and 0.50.

Table 5. Association of Myocardial Infarction With Duration of Estrogen Use

Estrogen Use	No. of Case Subjects	No. of Control Subjects	Odds Ratio*	95% Confidence Interval
Never	621	1274	1.00	Reference
Ever				
Duration, y				
>0-<1.8	95	267	0.77	0.58-1.02
1.8-<4.2	51	171	0.70	0.49-1.00
4.2-<8.2	52	145	0.74	0.51-1.06
≥8.2	31	117	0.60†	0.39-0.93
Current				
Duration, y				
>0-<1.8	40	101	0.91	0.60-1.38
1.8-<4.2	29	104	0.70	0.45-1.10
4.2-<8.2	33	103	0.65	0.42-1.01
≥8.2	24	103	0.55‡	0.34-0.88
Past				
Duration, y				
>0-<1.8	55	166	0.69	0.49-0.97
1.8-<4.2	22	67	0.70	0.41-1.18
4.2-<8.2	19	42	0.93	0.51-1.69
≥8.2	7	14	0.96§	0.36-2.52

*The risk for myocardial infarction was adjusted for age, year of identification, diabetes mellitus, angina, and current smoking.
†Trend, P=.35.
‡Trend, P=.05.
§Trend, P=.29.

The finding of a decreased risk for incident MI in association with increasing duration of estrogen use in women who were currently using estrogen did not differ significantly in subgroups of women defined by age (older vs younger than the median age of 70 years), angina, current smoking, or body mass index (a measurement of the weight in kilograms divided by the square of the height in meters) (above vs below the median of 25.7 kg/m^2).

COMMENT

In this population-based, case-control study, among current users of estrogen, longer duration of use was inversely associated with a risk for MI, with a 45% reduction in risk for those who had used estrogen for 8.2 years or more compared with those who had never used estrogen. Among subjects who had used estrogen in the past, no association of long duration with decreased risk was observed.

The strengths of this observational study include the use of population-based case subjects and control subjects, the completeness of case identification, the validation of case diagnoses, the comparable ascertainment of potential confounding factors, and the use of the GHC pharmacy database to assess hormone use in a comparable and unbiased fashion. Restriction, stratification, and adjustment were used to minimize the possibility of confounding. All subjects were enrollees in a health maintenance organization and thus had similar access to health care.

As an observational study, the case-control design also has several limitations. Subjects and their physicians selected hormone replacement therapy and its duration, which may have introduced bias. There may have been unknown or unmeasured confounding factors for which adjustment was not possible. Measurement error in the assessment or estimation of covariates and their severity may have resulted in incomplete adjustment and residual confounding. In this study, information on duration of hormone use was restricted to that obtained using pharmacy data. While this method ensures comparable and unbiased assessment of hormone use, it ignores hormone use that occurred during periods when women were not enrolled in the GHC.

To our knowledge, there is little information available in the literature about the association between increasing duration of estrogen replacement therapy and the risk for MI. Previous studies have been limited in either the number of MI events available for study[12,13] or the number of years for which estrogen exposure data were available,[14] or they have relied on self-reported duration of estrogen use.[15-20] For women who died of acute MI, according to categories of duration of estrogen use (nonusers, >0-3 years, 4-14 years, and ≥15 years), Henderson et al[16] reported relative risks of 1.00, 0.64, 0.60, and 0.52, respectively ($P<.05$, test for trend); these results are similar to those for incident MI in the present study. Others reported no association[17,19,20] or were inconclusive.[12,13,15]

Self-reported recall of the duration of postmenopausal hormone therapy is known to be problematic. In a study of women who had filled estrogen prescriptions for at least a consecutive 90-day period, according to the GHC pharmacy database, West and colleagues[21] found that only 24% of women interviewed 2 to 11 years later could provide the name of the estrogen therapy and the years that the therapy began and ended. Of those, only 68% provided a duration of therapy within 2 years of the duration according to the pharmacy database.[21] The level of accuracy was lower for women older than 65 years and for periods of exposure that occurred more than 7 years before the recall date. In studies of the risk for MI that rely on self-reported duration of estrogen therapy, the recall of the periods of estrogen exposure by elderly women for periods longer than 7 years in the past is critical.

Several authors[22-24] have discussed the potential for biased results in observational studies of the association between the risk for CHD and estrogen therapy, since women who receive estrogen have fewer risk factors for CHD than women who do not receive estrogen. However, the finding among the women who currently use estrogen that the amount of risk decreases with an increase in the duration of therapy is presumably less subject to such bias, since all women were currently using estrogen.

Women at increased risk of death or serious illness, including MI, may discontinue estrogen therapy.[25] This practice pattern may account partly for the finding in the present study that among women who used estrogen in the past, there was no association between a risk for MI and increasing duration of estrogen therapy. Other possible explanations for the lack of association between the duration of hormone therapy and the risk for MI in the women who had used estrogen in the past include the limited number of subjects and the limited range of duration of use available for study.

To our knowledge, there is little information about the relative importance of the many effects of estrogen in relation to the risk for CHD. The observation in the present study that adjustment for HDL cholesterol levels attenuated the association of duration of use with the risk for MI among the subjects who were currently using estrogen provides support for the hypothesis that the decreased risk for CHD is due, in part, to a long-term favorable effect on the lipid profile.

The findings of this study suggest that the long-term use of estrogen therapy, particularly in women currently using estrogen, is associated with a progressively declining risk for MI. Whether this association wanes in those who have discontinued estrogen therapy, as suggested by the results of the present study and seen in the well-established association of estrogen use with increased bone density,[26,27] remains to be established. Long-term estrogen therapy has been associated with an increased risk for breast cancer in some[28,29] but not all studies.[30,31] The findings from the present study that a decreased risk for MI is associated with long-term estrogen use should be considered together with other information about the benefits and risks when women and their physicians make decisions about hormone replacement therapy.

Accepted for publication November 21, 1996.

This study was supported by grants HL40628, HL43201, and HL53375 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

Presented at the American Heart Association 35th Annual Conference on Cardiovascular Disease Epidemiology and Prevention, San Antonio, Tex, March 10, 1995.

We thank Edward H. Wagner, MD, MPH, for his assistance in the design of this study and Cheri Anderson, Margaret L. Birdsall, MHA, Mary Grassley, Ellen Hresko, Betty Monson, Linda Page, Richard Schaadt, Jean G. Yee, MS, and Barbara E. Young, PhD, for their assistance with its conduct. We also thank the physicians, the study participants, and the medical records clerks at GHC of Puget Sound.

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