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ORIGINAL CONTRIBUTIONS

Prior to Use of Estrogen Replacement Therapy, Are Users Healthier than Nonusers?

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Observational studies have demonstrated that women who have used postmenopausal estrogen replacement therapy (ERT) are at reduced risk of coronary heart disease. The authors examined whether premenopausal women who subsequently elected to use ERT during menopause had a better cardiovascular risk factor profile prior to use than did nonusers. A total of 541 premenopausal women had their cardiovascular risk factors and psychosocial characteristics evaluated at study entry. After approximately 8 years, 355 women had become postmenopausal, and 157 women reported ERT use during the follow-up period (mean = 93.4 months). The authors compared the premenopausal characteristics of users with those of nonusers. Relative to nonusers, ERT users were better educated (63 vs. 81% with at least some college), and prior to the use of ERT had higher levels of high density lipoprotein (HDL) cholesterol (1.49 vs. 1.59 mmol/liter), HDL2 (0.50 vs. 0.57 mmol/liter), HDL3 (0.98 vs. 1.02 mmol/liter), leisure physical activity (5,122 vs. 7,158 Kjoules), and alcohol intake (7.5 vs. 9.7 g/day), and lower levels of apolipoprotein B (0.97 vs. 0.90 g/liter), systolic blood pressure (112.1 vs. 107.1 mmHg) and diastolic blood pressure (73.8 vs. 71.4 mmHg), weight (68.5 vs. 64.2 kg), and fasting insulin (9.10 vs. 7.66 μU/liter). Prior to use of ERT, in comparison with nonusers, subsequent users reported on standardized questionnaires that they more often exhibited Type A behavior, were more aware of their feelings, motives, and symptoms, and had more symptoms of stress. Women who elect to use ERT have a better cardiovascular risk factor profile prior to the use of ERT than do women who subsequently do not use this treatment during the menopause, which supports the hypothesis that part of the apparent benefit associated with use of ERT is due to preexisting characteristics of women who use ERT. This study underscores the widely recognized importance of randomized clinical trials to estimate the direct benefit of postmenopausal ERT for protecting women from cardiovascular disease. *Am J Epidemiol* 1996;143:971–8.

cardiovascular diseases; estrogen replacement therapy; menopause; risk factors

Observational studies of the risks and benefits of postmenopausal estrogen hormone replacement therapy (ERT) have demonstrated that women who have ever used ERT are at reduced risk of coronary heart disease relative to never users, even when statistical adjustments are included for the major cardiovascular risk factors or after excluding women with any major risk factors (1–3). Angiography studies of patients referred for suspected coronary disease find that ever users have a reduced risk of significant atherosclerosis. It is estimated that the risk for coronary disease is reduced by 44 percent among ever users compared with nonusers (4). Further, the estimated benefit of ERT use from observational data is partially eliminated when statistical controls are introduced for lipid levels, which suggests that the favorable effect of ERT

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Abbreviations: ERT, estrogen replacement therapy; HDL, high density lipoprotein; LDL, low density lipoprotein; PEPI Trial, Postmenopausal Estrogen/Progestin Interventions Trial.

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is due in part to alterations in lipid levels (1). Indeed, the findings of the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial are consistent with that hypothesis (5). Women randomly assigned to oral estrogen alone or in combination with progestin experienced a favorable change in high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and fibrinogen, but no change in systolic blood pressure and fasting insulin 2 hours post glucose load. These findings are consistent with existing observational studies of menopause (6, 7). Furthermore, human and animal studies support the hypothesis that estrogen may have an effect on hemostatic factors and promote vasodilation in diseased coronary arteries (8, 9).

Observational study designs are criticized because they are subject to selection bias. That is, patient or physician preferences might systematically result in patients with a preexisting good (or bad) prognosis for an outcome event being prescribed a treatment. In the case of ERT, if patients who have a better cardiovascular risk factor profile are recommended for this treatment, then the benefits of ERT for coronary disease may be overestimated in observational studies. Cross-sectional studies indicate that women who use ERT are better educated and thinner (10, 11). Low education and obesity are risk factors for coronary disease (12, 13).

The present prospective investigation compared the cardiovascular risk factors of premenopausal women who subsequently either used ERT or did not use ERT during peri- and postmenopausal years. We hypothesized that prior to use of ERT, users would exhibit a more favorable risk factor profile. In an effort to evaluate the role of patient preferences in determining use of ERT, we also compared the psychological characteristics of women who subsequently used ERT or did not use ERT.

MATERIALS AND METHODS

Study population

In 1983–1985, 541 premenopausal women were recruited to be in a study of menopausal changes in biologic and behavioral characteristics. These women had been contacted by letter in a mailing sent to randomly selected women aged 42–50 years with driver's licenses and who lived within selected zip codes in Allegheny County, Pennsylvania. Eligibility for the study was determined during a telephone interview and included the following criteria: age 42–50 years; menstrual bleeding within the last 3 months; no surgical menopause; diastolic blood pressure <100 mmHg; and no medications known to influence biologic risk factors under study, e.g., current transdermal or oral estrogens, lipid lowering, insulin, thyroid, antihypertensive, and psychotropic medications. Eighty-nine percent of women contacted agreed to the telephone interview; 60 percent of eligible women, i.e., 541 women, volunteered. No payment was offered for participation. The University Institutional Review Board approved the project protocol. Eligible participants were better educated than eligible nonparticipants; complete details regarding participant characteristics and recruitment are available elsewhere (14).

All 541 women completed the baseline examination described below, and then reported monthly via postcard (or via telephone interview for those who did not return postcards) their menstrual status and hormone use until they ceased cycling for 12 months or ceased cycling and began to use hormone replacement therapy that in combination totaled 12 months. At that point, they were scheduled for a postmenopausal examination and were followed thereafter on an annual basis.

As of October 1992, a total of 355 women had become naturally menopausal and had been reevaluated, and 185 used hormones sometime during the follow-up period between study entry and the most recent evaluation (mean follow-up period = 93.4 months, standard deviation = 8.7, range 39–106 months). Of the 185 women, 157 women had used or were using oral or transdermal estrogens (called ERT users), mainly in combination with progestin (n = 137). The remaining users were using progestins alone (n = 19), or vaginal creams on an irregular basis (n = 5). Four women reported that they used hormones between clinic evaluations, had discontinued use, but did not know what the hormones were. A total of 170 women reported that they had not used hormones during the follow-up period. The women in the cohort who had a surgical menopause (n = 32) were excluded because rates of hormone use differ dramatically by surgical versus natural menopause status (10). Thus, the final sample for the analyses reported herein was composed of 327 women, including 157 ERT users.

Protocol

The protocol included an initial telephone interview to determine eligibility, a home interview regarding medical history and blood pressure measurement, and a clinical baseline evaluation, which was scheduled for the morning after a 12-hour fast. The clinic evaluation included collection of a blood sample to measure serum lipoproteins and apolipoproteins; two measurements of blood pressure by the random zero-muddler method (15) by observers trained and certified accord-

ing to the Multiple Risk Factor Intervention Trial protocol (16); glucose loading (75 g) with blood sampling beforehand and 2 hours afterward; measurement of height and weight; a questionnaire about health-related behaviors, including level of physical activity (17) and alcohol consumption; a 24-hour food recall interview administered by a trained nutritionist with three-dimensional models of food portions; and a self-report inventory containing standardized tests of personality and behavior. This inventory included: 1) Beck Depression Inventory (18), extent of depressive symptoms during the previous 2 weeks; 2) Cohen Perceived Stress Scale, extent of symptoms of stress in the last 2 weeks (19); 3) the occurrence of 27 psychological and physical symptoms experienced during the previous 2 weeks drawn from a standard checklist of menopausal symptoms developed by Neugarten and Kraines (20); 4) the Self-Consciousness Inventory, with two subscales, Private, being aware of feelings, symptoms, motives, and Public, being aware of oneself in public situations (21); 5) Bortner Type A scale, personality style of being competitive and time urgent (22); and 6) feeling dissatisfied with one's job (23).

Women were evaluated after they became postmenopausal on an annual basis in a protocol similar to that above. Women also reported at that time whether or not they used hormone replacement therapy, its type, dosage, and duration for the previous year.

Laboratory assays and measurements

Levels of total serum cholesterol (24), total HDL cholesterol (25), HDL subfractions (HDL2 and HDL3) (26), triglycerides (27), and apolipoproteins (28) were measured by a lipid laboratory using the standards of the Centers for Disease Control and Prevention for total cholesterol. Low density lipoprotein (LDL) cholesterol levels were estimated with the Friedewald equation (29). The coefficients of variation (in percent) were 1.3, 2.1, 6.0, 1.7 for total, HDL, HDL3, and triglycerides, respectively. The coefficients of variation were 3.9 percent for apolipoprotein AI, 8.8 percent for apolipoprotein AII, and 9.8 percent for apolipoprotein B. Plasma glucose levels were determined by enzymatic assay (glucose analyzer, Instrument Co., Yellow Springs, Ohio), with coefficient of variation of 1.8 percent between runs. Because of skewed distributions, the triglyceride and insulin (30) values were log-transformed before analysis. The two measurements of blood pressure were averaged.

Data analysis

The levels of risk factors, symptoms, and personality are expressed as means ± standard error. Chi square or *t*-tests were used to compare the 157 users of ERT to the 170 nonusers. ERT groups were stratified by body mass index (above and below median of sample distribution) and educational attainment (at least a 4-year college degree vs. some college and high school degree or less). ERT group by body mass index or ERT group by education analyses of variance were conducted on those variables that significantly discriminated ERT users and nonusers. Stepwise logistic regression analyses, both forwards and backwards, were conducted predicting ERT use/never use, including those biologic and health behaviors that significantly discriminated ERT users and nonusers. Because the results for these analyses were the same, only the forward stepwise analysis is reported below. Two-tailed p values of less than 0.05 were considered significant.

RESULTS

Users and nonusers of ERT during the follow-up period were similar in age, marital status, and current employment at their premenopausal evaluation (table 1). However, women who used ERT were better educated and more often white than nonusers.

Cardiovascular risk factor profile prior to hormone use

Users and nonusers of ERT had similar levels of total and LDL cholesterol at study entry (table 2). However, women who subsequently used ERT had higher levels of total HDL cholesterol and HDL2 cholesterol, and lower levels of apolipoprotein B, at their premenopausal evaluation, relative to women who did not subsequently use ERT.

Users and nonusers of ERT differed on other cardiovascular risk factors prior to use of hormones (table

TABLE 1. Sociodemographic characteristics at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy, Pittsburgh, PA, 1983–1992

Characteristic	Subsequent user	Nonuser	*t*-test or χ^2 *p* value
No. of women	157	170	
Mean age (years) ± SE*	47.6 ± 0.1	47.9 ± 0.1	0.09
Married (%)	75.2	68.8	0.20
Nonwhite (%)	5.1	12.4	0.02
Education (no.)			0.004
Advanced degree	45	38	
College degree	42	36	
Some college	40	33	
No college	30	63	
Currently employed (%)	75.1	75.9	0.88

* SE, standard error.

TABLE 2. Mean ± standard error levels of serum lipids at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy, Pittsburgh, PA, 1983–1992

Characteristic	Subsequent user	Nonuser	*t*-test	*p* value
Cholesterol (mmol/liter)*				
Total	4.81 ± 0.07	4.83 ± 0.07	0.25	0.80
LDL†	2.79 ± 0.06	2.89 ± 0.06	1.12	0.27
HDL†	1.59 ± 0.03	1.49 ± 0.03	2.67	0.008
HDL2	0.57 ± 0.02	0.50 ± 0.02	2.30	0.02
HDL3	1.02 ± 0.01	0.98 ± 0.01	2.06	0.04
Apolipoproteins (g/liter)				
AI	1.44 ± 0.01	1.43 ± 0.02	0.77	0.44
AII	0.53 ± 0.01	0.52 ± 0.01	0.63	0.53
B	0.90 ± 0.02	0.97 ± 0.02	2.50	0.01
Triglycerides (mmol/liter)‡	0.93 ± 0.04	1.00 ± 0.04	1.32	0.19

* To convert cholesterol values to milligrams per deciliter, multiply by 38.67.
† HDL, high density lipoprotein; LDL, low density lipoprotein.
‡ To convert triglyceride values to milligrams per deciliter, multiply by 88.57.

3). Users of ERT had lower levels of systolic and diastolic blood pressure, fasting insulin, and weight than nonusers at study entry. Women who used ERT drank slightly more alcohol and engaged in more leisure time physical activity than did nonusers.

We have previously reported (14) that eligible women who agreed to participate were better educated than women who did not agree and that educational attainment was related to a more favorable cardiovascular risk factor profile in the full sample of women who entered into the study (i.e., the 541 women who enrolled at baseline). We wished to evaluate if the above differences in risk factors between ERT users and nonusers might be apparent in both the more and less educated women in our sample or if the above differences were due to other selection factors associated with patient or physician preferences, independent of educational attainment. Similarly, because being thin was related to a more favorable risk factor profile in the full sample (31), we wished to evaluate if the above risk factor differences (other than body mass index) might be best attributed to thin women being prescribed ERT.

Analysis by user/nonuser of ERT by 4-year college degree versus less than a 4-year college degree still showed that more and less educated users of ERT had more favorable levels of HDL cholesterol, blood pressure, fasting insulin, physical activity, and weight than did nonusers (table 4). This suggests that the better risk factor profile of hormone users is not attributed to better educated women using ERT.

Analysis by user/nonuser of ERT by above compared with below the median of the distribution of body mass index showed that users of ERT had lower levels of blood pressure and higher levels of physical activity than did nonusers (table 5). HDL cholesterol

TABLE 3. Mean ± standard error levels of other biologic characteristics and health behaviors at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy, Pittsburgh, PA, 1983–1992

Characteristic	Subsequent user	Nonuser	*t*-test or χ^2	*p* value
Blood pressure (mmHg)				
Systolic	107.1 ± 0.8	112.1 ± 1.1	3.73	<0.001
Diastolic	71.4 ± 0.6	73.8 ± 0.7	2.68	0.008
Glucose (mmol/liter)				
Fasting	4.81 ± 0.05	4.88 ± 0.07	0.95	0.35
Two-hour	5.03 ± 0.10	5.27 ± 0.14	1.43	0.15
Fasting insulin (μU/liter)	7.66 ± 0.44	9.10 ± 0.55	2.13	0.03
Height (m)	1.64 ± 0.005	1.63 ± 0.005	0.24	0.81
Weight (kg)	64.2 ± 0.9	68.5 ± 1.1	3.01	0.003
Alcohol intake (g/day)	9.7 ± 0.8	7.5 ± 0.8	2.01	0.05
Weekly physical activity (Kjoules)	7,158 ± 791	5,122 ± 369	2.33	0.02
Ever smoker (%)	61.8	55.0	1.53	0.22
Current smokers (%)	28.7	34.1	1.13	0.29

TABLE 4. Mean ± standard error levels of selected biologic characteristics and health behaviors at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy (ERT) according to educational attainment, Pittsburgh, PA, 1983–1992

Characteristic	≥4-year college degree		<4-year college degree		Main effect *p* value*	
	Subsequent user (*n* = 87)	Nonuser (*n* = 74)	Subsequent user (*n* = 70)	Nonuser (*n* = 96)	Education	ERT use
Cholesterol (mmol/liter)†						
HDL	1.63 ± 0.04	1.53 ± 0.05	1.56 ± 0.05	1.46 ± 0.03	0.06	0.02
HDL2	0.58 ± 0.03	0.56 ± 0.03	0.57 ± 0.04	0.46 ± 0.02	0.06	0.04
HDL3	1.05 ± 0.02	0.97 ± 0.02	0.99 ± 0.02	0.99 ± 0.02	0.28	0.05‡
Apolipoprotein B (g/liter)	0.87 ± 0.03	0.94 ± 0.03	0.93 ± 0.03	0.99 ± 0.03	0.06	0.02
Blood pressure (mmHg)						
Systolic	107.3 ± 1.16	110.0 ± 1.55	106.8 ± 1.13	113.6 ± 1.44	0.25	0.001
Diastolic	71.6 ± 0.87	72.4 ± 1.07	71.1 ± 0.85	74.9 ± 0.87	0.28	0.01
Fasting insulin (μU/liter)	7.1 ± 0.35	9.2 ± 0.97	8.4 ± 0.89	9.0 ± 0.63	0.52	0.04
Alcohol intake (g/liter)	7.9 ± 1.24	6.5 ± 1.39	11.2 ± 1.02	8.8 ± 0.81	0.01	0.09
Weekly physical activity (Kjoule)	8,364 (1,344)	5,122 (533)	5,658 (566)	5,121 (510)	0.11	0.03
Weight	62.9 ± 1.01	68.3 ± 1.65	65.8 ± 1.51	68.6 ± 1.50	0.28	0.005

* Significance levels from 2 (user/nonuser) by 2 (high/low educational attainment) analyses of variance; only the interaction term from HDL3 was statistically significant.
† To convert cholesterol levels to milligrams per deciliter, multiply by 38.67.
‡ Education × ERT use interaction term: $p < 0.05$.

TABLE 5. Mean ± standard error levels of selected biologic characteristics and health behaviors at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy (ERT) according to body mass index (kg/m²), Pittsburgh, PA, 1983–1992

Characteristic	Body mass index >24		Body mass index ≤24		Main effect *p* value*	
	Subsequent user (*n* = 59)	Nonuser (*n* = 90)	Subsequent user (*n* = 97)	Nonuser (*n* = 80)	Body mass index	ERT use
Cholesterol (mmol/liter)†						
HDL	1.46 ± 0.04	1.36 ± 0.03	1.68 ± 0.04	1.63 ± 0.04	0.001	0.06
HDL2	0.47 ± 0.03	0.42 ± 0.02	0.64 ± 0.03	0.60 ± 0.03	0.001	0.15
HDL3	1.00 ± 0.02	0.94 ± 0.02	1.04 ± 0.02	1.03 ± 0.02	0.001	0.11
Apolipoprotein B (g/liter)	1.00 ± 0.04	1.02 ± 0.03	0.84 ± 0.02	0.91 ± 0.03	0.001	0.08
Blood pressure (mmHg)						
Systolic	109.5 ± 1.28	115.6 ± 1.34	105.5 ± 1.04	108.2 ± 1.58	0.001	0.001
Diastolic	74.1 ± 0.97	76.2 ± 0.90	69.7 ± 0.75	71.2 ± 0.97	0.001	0.05
Fasting insulin (μU/liter)	10.0 ± 1.03	11.6 ± 0.93	6.2 ± 0.26	6.3 ± 0.30	0.001	0.23
Alcohol intake (g/liter)	7.3 ± 1.09	6.1 ± 0.81	11.3 ± 1.15	9.0 ± 1.32	0.002	0.12
Weekly physical activity (Kjoule)	5,798 (622)	4,804 (513)	8,040 (1,218)	5,484 (530)	0.09	0.04

* Significance levels from 2 (user/nonuser) by 2 (high/low body mass index) analysis of variance; no interactions were statistically significant.
† To convert cholesterol values to milligrams per deciliter, multiply by 38.67.

and apolipoprotein B levels in ERT groups stratified by body mass index showed that users had more favorable levels than nonusers, but the comparisons between ERT users and nonusers were no longer statistically significant, p's < 0.08. These findings suggest that differences in baseline body mass index between users and nonusers account in part for their baseline differences in lipids and insulin levels. However, the favorable blood pressure and physical activity level of ERT users is apparent in both women of high and low body mass index in this sample.

Psychological profile prior to hormone use

Because the use of ERT is jointly determined by physician and patient preferences, we examined if psychological characteristics differed at study entry of women who subsequently did or did not ever use ERT. Relative to nonusers, women who were users were more Type A and self-conscious about their private feelings, thoughts, and symptoms; more contented with their paid work; and reported more stress symptoms prior to the use of ERT (table 6).

TABLE 6. Mean ± standard error levels of psychological characteristics at premenopausal examination of subsequent users and nonusers of estrogen replacement therapy, Pittsburgh, PA, 1983–1992

Characteristic	Subsequent user	Nonuser	*t*-test	*p* value
Type A behavior	201.5 ± 3.0	188.0 ± 2.9	3.20	0.002
Self-consciousness				
Private	17.5 ± 0.4	16.0 ± 0.4	2.39	0.02
Public	12.4 ± 0.4	11.5 ± 0.3	1.68	0.09
Job dissatisfaction	7.3 ± 0.2	7.9 ± 0.2	2.12	0.04
Symptoms in previous 2 weeks				
Beck depression inventory	4.7 ± 0.4	4.2 ± 0.4	0.87	0.39
Cohen perceived stress	12.5 ± 0.3	11.5 ± 0.3	2.38	0.02
Menopausal	6.7 ± 0.2	6.0 ± 0.3	1.43	0.15

DISCUSSION

Because of the reported beneficial effects in observational studies of ERT on risk for cardiovascular disease, the present investigation compared the premenopausal biologic and psychological characteristics of premenopausal women who subsequently chose to use ERT with the characteristics of women who chose not to use ERT during menopause. Results showed that women who subsequently used ERT had a better cardiovascular risk factor profile than nonusers of ERT, prior to the use of exogenous hormones. More specifically, ERT users had higher levels of HDL and HDL2 cholesterol, and lower levels of fasting insulin, systolic and diastolic blood pressure, apolipoprotein B, and weight; they drank more alcohol, took more leisure-time physical exercise, and were better educated, relative to nonusers of ERT. To our knowledge, this study is the only study to have analyzed detailed prospective data on the premenopausal characteristics of subsequent users of ERT.

Further analysis of the premenopausal characteristics of users and nonusers of estrogen stratified by educational attainment and body mass index suggests the physician or patient preferences that could have determined the hormone group differences. Although stratification of user groups by educational attainment did not substantially alter the results, stratification by body mass index reduced significant hormone group differences to nonsignificant trends for levels of HDL and HDL2 cholesterol, apolipoprotein B, insulin, and alcohol ingestion. This suggests that more favorable lipid, apolipoprotein, and insulin levels of subsequent users of ERT were in part due to thinner women being more likely to subsequently use ERT.

Why might weight determine subsequent use of ERT? Obese postmenopausal women tend to have higher levels of circulating estrogens than thin women due to the conversion of androstenedione to estrone in fat tissues (32). In consequence, obese women may have fewer symptoms and seek treatment less often. Physicians may prescribe ERT less often for obese women than thin women, and obese women, who have a worse cardiovascular risk factor profile than thin women, would predominantly be categorized as non-ERT users.

Neither stratification by educational attainment nor weight altered the lower systolic and diastolic blood pressure among users of estrogens nor did stratification by educational attainment alter the lower weight among users of estrogens. The more favorable weight and blood pressure levels of subsequent users of ERT then may be due to other physician/patient preference factors correlated with blood pressure.

The preexisting psychological characteristics of women who subsequently used hormones may aid in identifying possible patient factors that determine hormone use. Hormone users reported on standardized tests being more Type A and aware of their feelings and symptoms, and having more symptoms of stress than nonusers reported. Other things being equal, these characteristics should make women more aggressive in seeking treatment and more aware of their symptoms during the menopausal transition, which, in turn, should affect their use of hormones.

These findings might also suggest that ERT users would be at higher risk for coronary disease because of their tendencies to be Type A and perceive high levels of stress symptoms. Arguing against this interpretation is that Type A does not appear to be a risk factor for myocardial infarction or sudden death in women, although it was a risk factor for angina in the Framingham Heart Study (33). Similarly, there are no data associating perceptions of stress symptoms and coronary disease in women, although there are data associating reports of important stressful life events, e.g., loss of a significant other, and coronary disease (34).

Taking our findings together, we suggest that women who use ERT in the early postmenopausal period have a better cardiovascular risk factor profile, prior to hormone use and when still premenopausal,

than do nonusers of hormones. Further, although the magnitude of group differences in risk factor profile is specific to our population, we suggest it is instructive to consider their potential effect on the estimates of the beneficial effects of estrogen use obtained in observational studies. For example, we found that prior to any hormone use, the difference in level of HDL cholesterol between users and nonusers of hormones was 0.100 mmol/liter. In the Framingham Heart Study, an increment of 0.026 mmol/liter (1 mg/dl) in HDL cholesterol level was associated with a decrement in risk of coronary disease by 3 percent and in risk of cardiovascular death by 4.7 percent in women (35). If this relation can be applied here, there should be a 11.5 percent difference in risk of coronary disease and 18.0 percent difference in risk for cardiovascular death between users and nonusers, attributable to preexisting characteristics of the women and not due to the use of hormones. A second example is the 2.4 mmHg difference in diastolic blood pressure between users and nonusers of hormones. Meta-analysis of randomized trials of hypertensives suggests a 2–3 percent decline in risk of myocardial infarction for 1 mmHg decline in diastolic blood pressure (36). If this relation can be applied to women, there should be a 5 percent reduction in risk for myocardial infarction in users, relative to nonusers, attributable to preexisting characteristics of the women and not due to the use of hormones.

An important issue is whether statistical adjustment for risk factor differences between users and nonusers of ERT can account for the probable selection bias for women who will take ERT. For example, adjustment for educational attainment in analysis of the effects of ERT does not mean that other variables related to education and risk of disease are now "adjusted for" in users and nonusers. We cannot presume that better educated women who take ERT are similar in all characteristics related to cardiovascular disease to the less educated women who take ERT.

Similarly, adjustment for risk factors measured at the time of study entry, which usually takes place in women after or even during menopause, clearly does not adjust for important risk factors or risk factor changes from the pre- to the postmenopause. The development of atherosclerosis may be determined in part by the risk factor levels early in life, which may not be highly correlated with the postmenopausal levels. We recently reported that premenopausal risk factor levels correlated as high and sometimes higher with extent of carotid atherosclerosis measured 5–8 years after menopause, as did concurrent or early postmenopausal measures of risk factors (37). The reduced risk of cardiovascular disease associated with ERT may not be duration dependent. For example, in the Nurses Health Study, the relative risk among current users of ERT for major coronary disease was 0.5 and in former users the relative risk was 0.9 (38). This suggests that the beneficial effects of estrogens might be lost fairly rapidly following cessation of ERT or that adherence to therapy, whether for a short or long duration, is a marker for reduced risk of disease and not necessarily the direct effect of ERT.

The recently completed PEPI Trial (5) recruited women with a mean age of 56.1 years, many of whom had previously been on hormone replacement therapy. At the end of the 3-year study, 36 percent of women on hormones who had an intact uterus were not taking any estrogen therapy and the cumulative percent of women with a uterus who were unable to continue unopposed estrogen therapy for any reason was 55 percent. These results point to the potential for a selection bias for continued estrogen therapy among women with an intact uterus, and studies that compare long-term users of estrogen therapy and nonusers may be suspect unless restricted to women who have had an artificial menopause or hysterectomy.

In sum, our results suggest that users of ERT have a better cardiovascular risk factor profile prior to the use of ERT than do nonusers during the early postmenopausal period. This suggests that there are important selection biases for hormone therapy that need to be considered in interpreting the results of observational studies, even in those that use excellent statistical controls and are homogeneous in nature. Nonetheless, the fact that selection biases for use of hormones exist does not preclude the likely benefit of ERT on both cardiovascular risk factors and disease. As has been widely recognized, the risks and benefits of ERT need to be evaluated in ongoing randomized trials. Most likely there are subsets of women who will benefit and others who will not benefit from use of ERT. Only trials, such as the hormone arm of the Clinical Trial included in the Women's Health Initiative, will allow definitive conclusions about the benefits and liabilities of long-term use of exogenous postmenopausal estrogen.

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