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Are Long-term Hormone Replacement Therapy Users Different from Short-term and Never Users?

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The characteristics that differentiate long-term (≥ 10 years) hormone replacement therapy (HRT) users from short-term (< 10 years) users and nonusers are not well documented. The epidemiology of long-term HRT use was investigated within a random sample survey of 703 women aged 50–80 years who were members of Group Health Cooperative (GHC) of Puget Sound. Women who had been menopausal for ≥ 10 years comprised the study population. Long-term HRT users (29.4 percent) were compared with short-term (28.1 percent) and never users (42.5 percent). The authors examined the association between duration of HRT use and demographic characteristics, personal and family medical history, menopausal symptoms, information used in decision making, attitudes toward HRT, provider encouragement to use HRT, and GHC utilization. Compared with never users, the strongest correlates of long-term HRT use were having a hysterectomy before or after menopause, positive attitudes espousing the benefits of HRTs, and perceived provider encouragement to use HRT. Long-term HRT use was not associated with educational attainment, ethnicity, body mass index, health status, physical activity, or family medical history. Correlates commonly associated with HRT use, such as higher education, greater physical activity and functioning, and lower chronic disease comorbidity, did not significantly distinguish long-term from short-term users. *Am J Epidemiol* 1999;149:275–81.

estrogen replacement therapy; estrogens; menopause; selection bias

Epidemiologic studies consistently show that the benefits of hormone replacement therapy (HRT) in reducing risks of fractures and heart disease are greatest for long-term current users (1, 2). However, the beneficial effects of HRT reported in many observational studies have been criticized as overestimates because of the potential “healthy user bias” (3–9). Identifying correlates of long-term HRT use is important to help understand why women persist in using HRT. This, in turn, can assist in exploring the potential biases in observational studies of HRT.

A large body of literature exists which suggests that women who use HRT are healthier than women who do not (3–8). On this basis, women who are long-term HRT users may be healthier than women who initiate and then discontinue HRT. Characteristics that differ-

entiate long-term (≥ 10 years) HRT users from short-term (< 10 years) and never users have not been well documented. To our knowledge, no one has reported correlates of long-term HRT use by limiting comparison groups to women who have been postmenopausal for at least 10 years and therefore have had equal opportunity for long-term use. This study was undertaken to better understand characteristics of women who elect to take HRT for many years.

MATERIALS AND METHODS

Study population

The EnPower Women’s Survey was conducted at Group Health Cooperative (GHC) of Puget Sound. This staff model health maintenance organization provides medical care to over 370,000 people in western Washington State, including approximately 53,000 women aged 50–79 years. GHC members are representative of the underlying population of Seattle, Washington, with the exception of a slightly higher level of education; they are the same with respect to ethnicity and socioeconomic status. The survey was designed to examine women’s preventive health behaviors and decision-making in four main areas: HRT, colorectal cancer screening, smoking, and physical activity. The methodology used for sampling has

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Abbreviations: CI, confidence interval; GHC, Group Health Cooperative; HRT, hormone replacement therapy; MOS, Medical Outcomes Study, OB/GYN, obstetrician-gynecologist; OR, odds ratio.

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been previously described (10). Briefly, women who were enrolled at GHC for at least 2 years prior to January 1, 1995 and who were aged 50–79 years were eligible. Three GHC clinics with the highest minority representation were oversampled in a three-to-one ratio in an effort to increase representation of minority women. Of the 1,520 randomly selected women, 125 were ineligible for one of the following reasons: language or hearing problems too severe to complete the interview ($n = 39$), too ill ($n = 27$), disenrolled from GHC ($n = 24$), no identifiable telephone number ($n = 19$), deceased ($n = 11$), no telephone ($n = 3$), or out-of-town during the survey period ($n = 2$). Of the 1,395 eligible women, 1,119 (80.2 percent) agreed to participate and completed computer-assisted telephone interviews between June and November 1995.

Women were eligible for these analyses if at least 10 years had elapsed between the onset of menopause and their study interview ($n = 718$). The onset of menopause was defined as either the age when menstrual periods had been absent for at least 12 months or the age at hysterectomy for women who reported a surgical menopause. All women had the opportunity for long-term HRT use. Women with missing data on duration of HRT use ($n = 15$) were excluded from the analysis, leaving a final sample of 703.

Variables

HRT use was ascertained from a combination of women's self-reported HRT use and GHC computerized pharmacy data. Never users were women who reported not having used HRT for longer than 3 months at any time. For women who were self-reported current users at the time of interview, length of HRT use was calculated by subtracting their current age from the age they reported that they started taking HRT. Among self-reported past HRT users, those who reported having taken HRT for at least 3 months but less than 10 years were classified as short-term users and women with 10 or more years of use were considered long-term users. This was based on self-reported duration of HRT combining all episodes of use, including intermittent and continuous use. Data from self-reported current users ($n = 262$) who reported filling their prescriptions at GHC were compared with computerized pharmacy data. Of these women, 24 (9.6 percent) had no evidence of filling any prescriptions for HRT at GHC and therefore were classified as never users.

Agreement rates between medication information collected from manual sources, such as medical charts, and GHC's computerized pharmacy data are between 89 and 100 percent (11). GHC has found that between 93 and 96 percent of subscribers fill all their prescriptions at GHC pharmacies (11).

Demographic characteristics including age, marital status, ethnicity, and education level were obtained during the telephone interview. Body mass index was calculated from self-reported height and weight measurements. Women were asked about the historical presence and severity of five menopausal symptoms: hot flashes, memory loss or difficulty concentrating, depression, night or day sweats, and trouble sleeping or awaking too early. Self-rated health was based on the question from the Medical Outcomes Study (MOS) SF-36 health scale, "Would you say that in general your health is excellent, very good, good, fair, or poor?" (12). Women were asked if they had ever had a doctor diagnosis of heart disease, hypercholesterolemia, hypertension, diabetes mellitus, bone fracture after age 50 years or kyphosis, colon cancer or colorectal polyps, and breast cancer. Family history of the same conditions in any first-degree relative was also asked. To control for the presence and severity of comorbid conditions, we relied on the GHC Chronic Disease Score. This score uses empirically derived weights based on age, sex, and 6 months of pharmacy data (medications used for the treatment and management of chronic conditions) to predict total health care costs in dollars for a 6-month period (13, 14). For example, a 60-year-old woman with hypertension and hypercholesterolemia would receive a score of \$950, whereas a 60-year-old disease-free woman would receive a score of \$593, and the score for a 60-year-old woman with diabetes would be \$1,701. The Chronic Disease Score has been demonstrated to be highly predictive of death, hospitalization, and ambulatory utilization (13). The MOS physical functioning scale (12, 15) asks questions that measure a person's ability to perform 10 typical daily activities; these are scored into a summary scale that ranges from 0 (substantial limitations in self-care and physical activity) to 100 (able to do vigorous activities without limitations) (15).

The survey measured several preventive health behaviors. From self-reported data, women were characterized as current, past, or never smokers. Physical activity, other than regular job duties, was measured using two questions, "How many times did you exercise or participate in regular physical activity during the past month?" and "When you took part in these activities, for how many minutes or hours per day did you usually keep at it?" From these two questions, number of hours of physical activity per day was calculated. Daily calcium supplementation refers to supplementation with calcium or Tums daily or almost every day at the time of the interview. Recency of last routine well visit was reported by women as "within the past year, one-to-two years ago, two-to-five years ago, or more than five years ago." Responses were collected and then dichotomized (≤ 2 years or > 2 years).

Number of mammograms in the past 5 years was collected by self-report and classified into four groups: none, one, 2–5, ≥ 6 mammograms. Computerized provider records were used to determine whether women had visited an obstetrician-gynecologist (OB/GYN) in the past 2 years.

Women were asked to indicate the degree to which their provider encouraged them to take HRT (not at all encouraging, neither encouraging nor discouraging, or somewhat or very encouraging). Women's attitudes about using HRT were assessed using a six-item scale ($\alpha = 0.76$) with scores ranging from 6 to 30, with higher scores indicating more favorable attitudes toward taking HRT (16). Scores were then trichotomized into tertiles (negative, neutral, or positive) based on the distribution of the entire cohort (see Appendix table for scale items and scoring). The authors also collected data about major sources of information that women claimed helped them decide whether or not to take hormones (for example, advice from friends or provider or things they had seen or read).

Statistical methods

Proportions for characteristics examined were compared by category of HRT duration (never, short-term, or long-term). After adjusting for age by the direct method, using the overall study population as the standard, differences in women by HRT duration were assessed using chi-square statistics for dichotomous and categorical variables and analysis of variance for continuous variables. Logistic regression was conducted to examine duration of HRT use in relation to groups of variables that were related to one another, such as demographic characteristics, personal medical history, and health history. All models included age. Separate models were used for long-term versus never users, short-term versus never users, and long-term versus short-term users. Women's attitudes were excluded from the multivariate analysis because their overwhelming association with HRT duration did not allow for exploration of other potentially important correlates. Variables that were significantly associated with HRT use from the group models (0.05 level, two-tailed) were included in a multivariate model. Women who had a hysterectomy had different characteristics associated with duration of use than women with intact uteri; therefore, models were also stratified on hysterectomy status. The final multivariate model included variables significantly related to long-term HRT use among all women or among women with or without a hysterectomy. Results presented are limited to differences between long-term and never users. Stratification by hysterectomy resulted in too few numbers to support a large multivariate analysis of short-term versus long-term users.

RESULTS

Women ranged in age from 50 to 80 years. Long- and short-term users were significantly younger than never users; mean ages were 66.3, 66.5, and 69.0 years, respectively. Long-term users were significantly more likely to be married and to have had a surgical menopause and oophorectomy than were never or short-term users (table 1). Women who had a hysterectomy were significantly more likely to be married and to take HRT for a longer duration and were younger than women with intact uteri (data not shown). There were no differences in education, smoking status, Chronic Disease Score, exercise, or body mass index by hysterectomy status.

Menopausal symptoms were reported more frequently by long-term users, followed by short-term users and then never users (table 1). Significant differences in ever-reported symptoms were seen only between long-term and never users. The most commonly reported symptoms were hot flashes followed by night or day sweats.

Age-adjusted health behaviors by duration of HRT use are described in table 2. Long-term users stood out on three important measures of health behavior. They were less likely to smoke, more likely to see their provider, and more likely to get mammograms. Long-term users were more likely to have had a well visit in the past 2 years (92.2 percent) than never users (82.9 percent), but no difference was seen for short-term users (89.1 percent). No differences were found by duration of HRT use in the mean number of hours of physical activity per day, the proportion who reported taking a calcium supplement, number of OB/GYN visits in the past 2 years, MOS physical functioning scale, or Chronic Disease Score. Unopposed estrogen was the predominant form of HRT, however short-term users were more likely to have taken combined therapy (39.4 percent) than long-term users (24.6 percent). When participants were compared by personal medical history, the only significant difference was observed for hypertension; 48 percent of long-term, 44.1 percent of short-term, and 36.2 percent of never users reported that they had the condition.

The strongest correlates of HRT use were women's attitudes about HRT and provider interactions (discussions about and encouragement to use HRT) (table 3). Long-term users were significantly more likely to have positive attitudes toward HRT than were short-term or never users, 77.9 percent, 31.1 percent, and 8.7 percent, respectively. Similarly, there were significant differences in perceived provider encouragement to use HRT. Fifty-two percent of long-term users reported that their provider was somewhat or very encouraging, compared with 11.5 percent for never users. Long-term users and never users were more likely to report discussions with

TABLE 1. Selected characteristics by duration of hormone replacement therapy use: the EnPower Study, 1995, Group Health Cooperative of Puget Sound, Washington State

Characteristic	Never (n = 300)	Short-term (n = 196)	Long-term (n = 206)
Age (years) (%)†,‡			
50–59	10.7	25.4	20.4
60–69	37.0	28.4	44.7
70–80	52.3	46.2	35.0
White (%)	89.3	86.8	91.3
Education (%)			
Less than high school	13.7	10.7	8.3
High school graduate	30.8	30.1	32.0
College or graduate school	55.5	59.2	59.7
Married (%)*	52.7	56.4	65.5
Body mass index, mean (kg/m ²) (SD¶)	27.1 (5.5)	26.5 (5.5)	26.7 (4.8)
Hysterectomy (%)†,§			
None	67.7	55.3	22.3
Before menopause	26.3	37.6	70.9
After menopause	6.0	7.1	6.8
Oophorectomy (%)†,§	9.2	15.5	38.8
Menopausal symptoms			
Hot flashes†	71.1	81.2	81.9
Night/day sweats†	43.6	57.4	62.9

Long-term user versus never user: * $p < 0.05$, † $p \leq 0.001$.

Long-term user versus short-term user: ‡ $p < 0.05$; § $p \leq 0.001$.

¶ SD, standard deviation.

TABLE 2. Age-adjusted health behaviors by duration of hormone replacement therapy (HRT) use: the EnPower Study, 1995, Group Health Cooperative of Puget Sound, Washington State

Health behavior	Never (n = 300)	Short-term (n = 196)	Long-term (n = 206)
HRT use (%)‡			
Unopposed estrogen		60.5	75.3
Estrogen and progesterone		39.4	24.6
HRT use duration, mean years (SD¶)§		2.9 (2.5)	19.9 (7.8)
Smoking (%)*			
Current	12.7	11.8	8.1
Past	37.2	38.4	49.7
Never	50.1	49.7	42.2
Regular physical activity, mean hours/day (SD)	1.2 (0.6)	1.2 (0.5)	1.1 (0.5)
Currently using calcium supplements (%)	53.1	60.7	60.7
No. of mammograms (past 5 years)†			
0	13.2	5.4	3.1
1	9.8	9.9	7.7
≥2	76.9	84.6	89.1
Clinic visits in past 2 years			
Well visit (%)*	82.9	89.1	92.2
Obstetric-gynecologist visit (%)	5.3	10.7	8.2
MOS¶ physical functioning scale#, mean (SD)	73.1 (15.6)	75.9 (13.9)	71.2 (15.7)
GHC¶ Chronic Disease Score**, mean (SD)	2,006 (1,151)	1,882 (686)	2,190 (907)
Personal medical history			
Coronary heart disease	9.4	11.8	7.1
Hypercholesterolemia	36.3	39.1	36.0
Hypertension‡	36.2	44.1	48.0
Diabetes mellitus	12.9	9.6	9.1
Fracture/kyphosis	31.2	35.3	28.7
Breast cancer	10.5	6.3	9.0

Long-term user versus never user: * $p < 0.05$, † $p \leq 0.001$.

Long-term user versus short-term user: ‡ $p < 0.05$; § $p \leq 0.001$.

¶ SD, standard deviation; MOS, Medical Outcome Study; GHC, Group Health Cooperative.

MOS physical functioning scale (range lowest to highest = 1–100).

** GHC Chronic Disease Score (range lowest to highest = 395–25,674).

TABLE 3. Age-adjusted women's attitudes toward hormone replacement therapy (HRT), their perception of provider encouragement to use HRT, and sources of information about HRT, by duration of HRT use: the EnPower Study, 1995, Group Health Cooperative of Puget Sound, Washington State

	Never (n = 300)	Short-term (n = 196)	Long-term (n = 206)
Women's attitudes toward HRT (%) ^{‡,†}			
Negative	51.6	26.4	3.9
Neutral	39.6	42.5	18.1
Positive	8.7	31.1	77.9
Provider encouragement to use HRT (%) ^{*,‡}			
Not at all encouraging	50.3	33.9	13.7
Neither encouraging nor discouraging	38.1	24.8	34.2
Somewhat encouraging/very encouraging	11.5	41.3	52.0
Sources of information about HRT (%)			
Reading materials (newspaper, magazines, books, pamphlets)	38.8	39.0	38.1
Friends*	14.3	10.7	8.3
Discussions with health care providers ^{‡,†}	45.9	72.4	83.4

Long-term user versus never user: * $p < 0.05$, † $p \leq 0.001$.

Long-term user versus short-term user: ‡ $p < 0.05$.

health care providers and friends, respectively, as major sources of information used in HRT decision making.

Long-term users who had undergone a hysterectomy were significantly leaner (odds ratio (OR) = 0.9; 95 percent confidence interval (CI) 0.8–1.0) and were 2.2 times more likely to have hypertension (95 percent CI 1.0–4.7) than never users (table 4). Long-term users with intact uteri were significantly less likely to have hypercholesterolemia (OR = 0.3; 95 percent CI 0.1–0.8), but were 3.1 times more likely to have night or day sweats (95 percent CI 1.1–8.2) than were never users. Among women with and without hysterectomy, long-term users were significantly more likely to report encouragement from their provider to use HRT and discussions with their provider as important factors in their decision to use HRT.

Some differences found between long- and short-term users overlapped with those seen for long-term and never users (data not shown). A positive association was seen for positive provider encouragement to use HRT and for provider being a major source of information used for decision making about HRT, although the magnitude of the association was smaller than that seen for long-term versus never users. While women reported using HRT for menopausal symptoms, there were no differences in reported symptoms between long- and short-term users. Prior to stratification by hysterectomy, a significant association was seen for long-term users who reported that they used HRT for prevention of osteoporosis.

DISCUSSION

The authors conducted a study to examine the correlates of long-term HRT use. Having had a hysterectomy either before or after natural menopause, positive attitudes espousing the benefits of HRT, and provider

interactions were the strongest correlates of long-term HRT use. Duration of HRT use was not correlated with educational attainment, ethnicity, health status (GHC Chronic Disease Score, MOS physical functioning scale), physical activity, or personal or family medical history—with the exception of personal history of hypertension and hypercholesterolemia.

Several studies have looked at correlates of HRT use (3–6, 16–19), where the focus has varied from correlates of initiation (5, 19, 20) to correlates of continuation and compliance (6, 7, 17, 18, 20). In the continuation and compliance studies, duration of HRT use has been examined primarily by characterizing women as current or past users. Because the characteristics of current users may not adequately describe long-term users, the focus of our study was on duration of HRT use.

Our multivariate results were stratified on hysterectomy status (ever vs. never) rather than on surgical as opposed to natural menopause, because the data demonstrated a stronger association with duration of HRT use among women who had ever had a hysterectomy than among women who had a surgical menopause. The strong association in our data between hysterectomy and long-term HRT use is consistent with findings from other studies that have reported hysterectomy as one of the strongest correlates of HRT use (2, 6). Lancaster et al. (6) identified a cohort of 1,482 HRT users (>1 year) aged 45–64 years and compared them with 1,482 nonuser controls. The only differences were found among women with an intact uterus, where HRT users were of slightly higher social class (measured by the occupation of partner) and were more likely to have had a mammogram. Cauley et al. (2) examined determinants of current, past, and never estrogen replacement therapy use in 9,704 non-black women. Among women with a surgi-

TABLE 4. Odds ratios (OR) and 95% confidence intervals (CI) comparing long-term hormone replacement therapy (HRT) users to never users for all women and for women by hysterectomy status: the EnPower Study, 1995, Group Health Cooperative of Puget Sound, Washington State

Characteristic	All women (n = 474)		Hysterectomy (n = 244)		No hysterectomy (n = 230)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)						
50–59	1.0		1.0		1.0	
60–69	1.0	0.5–2.1	1.5	0.6–3.8	0.6	0.2–2.1
70–80	0.6	0.3–1.2	0.7	0.3–1.8	0.4	0.1–1.3
Personal medical history						
Hypertension	2.0	1.2–3.4*	2.2	1.0–4.7*	1.9	0.8–4.5
Hypercholesterolemia	0.9	0.6–1.5	1.9	0.9–3.9	0.3	0.1–0.8*
Body mass index (kg/m ²)	0.9	0.9–1.0*	0.9	0.8–1.0*	1.0	0.9–1.0
Menopausal symptoms						
Hot flashes	1.4	0.7–2.7	1.5	0.6–3.7	1.2	0.4–4.1
Night or day sweats	1.8	1.0–3.2	1.3	0.6–3.0	3.1	1.1–8.2*
Source of information						
Provider	4.6	2.7–8.0†	5.5	2.6–11.6†	4.4	1.7–11.1*
Mammograms (past 5 years)						
None	1.0		1.0		1.0	
1	2.8	0.7–10.8	3.9	0.6–24.9	2.0	0.3–13.5
>2	2.8	1.0–8.3	4.7	1.1–21.2	1.1	0.3–4.6
Provider encouragement to use HRT						
Not at all encouraging	0.2	0.1–0.4†	0.1	0.1–0.3†	0.2	0.1–0.6*
Neither encouraging nor discouraging	1.0		1.0		1.0	
Somewhat encouraging/very encouraging	2.4	1.2–4.8*	1.6	0.6–4.0	4.7	1.5–14.7*
Hysterectomy	6.5	3.9–10.8†				

* $p < 0.05$.† $p < 0.001$.

cal menopause, current users were significantly younger, had more education, were leaner, and were more likely to have consumed alcohol than never users. Younger age was the only difference seen between current and past users among women with surgical menopause. Among women who had a natural menopause, similar results were reported, but osteoporosis and higher levels of physical activity were more common among users.

Results from our study are limited by the cross-sectional study design and by the potential of HRT use to influence certain correlates, such as Chronic Disease Score and personal medical history. At the same time, this study had many strengths. Our random sample came from a well-defined community population. The survey yielded a high response rate and was designed to examine factors that might influence women to use HRT that are not typically assessed, such as provider interaction and women's attitudes. Nevertheless, few variables were found to be strong correlates of long-term use.

The authors can only speculate as to why there were not many significant differences between short- and long-term users. On the whole, the population of Seattle is more homogenous than the populations of other cities in the United States. Furthermore, because the study was carried out in a health maintenance organization, the variability owing to health care sys-

tems and access is presumably reduced. Finally, although the categories for short- and long-term use were mutually exclusive, many women were using HRT at the time of the interview. Therefore, some short-term users could go on to become long-term users. Thus, we would not expect these two groups of women to be completely dissimilar.

Our results emphasize the critical roles in long-term continuation of HRT played by women's attitudes about HRT as a medical treatment for prevention and by their interactions with providers (encouragement to use and discussions about HRT). In fact, long-term HRT use may be more related to women's attitudes and provider interactions than to socio-demographic factors or health status that typically characterize current users. Correlates of HRT duration identified in this cross-sectional study cannot be assumed to predict who will go on to become long-term HRT users, but the correlates can be used to characterize women who remain on HRT for 10 or more years.

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APPENDIX TABLE. Percent distribution of responses to questions that comprise the attitudes scale* : the EnPower Study, 1995, Group Health Cooperative of Puget Sound, Washington State

	Strongly agree 1	Agree 2	Neither agree nor disagree 3	Disagree 4	Strongly disagree 5
A woman who is bothered by menopausal symptoms (such as severe hot flashes) should take hormone pills	6.4	57.7	1.3	16.0	18.7
Natural approaches for menopausal problems, such as nutrition, vitamins, and exercise, are better than taking hormone pills	1.4	19.9	10.8	16.5	42.8
I can reduce my risk of bone fractures by taking hormone pills for many years	4.4	41.7	1.7	20.5	31.7
I can protect myself from heart disease by taking hormone pills for many years	2.0	27.9	2.3	28.7	39.1
Taking hormone pills for many years does not make sense to me	5.4	36.7	6.1	9.2	42.5
I worry that taking hormone pills could increase my risk of getting breast cancer	3.1	36.7	7.5	9.8	42.8

* Attitudes scale $\alpha = 0.76$, by attitude and range: negative, 6-16; neutral, 17-20; positive, 21-30.