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Medical Care Costs Associated with Postmenopausal Estrogen Plus Progestogen Therapy

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ABSTRACT

Objective: To investigate the medical management costs of estrogen plus progestogen hormone therapy (HT) among postmenopausal women taking HT primarily as a preventive treatment for osteoporosis.

Design: Retrospective longitudinal comparative analysis of HT users and demographically matched nonusers using administrative databases on physician services, hospital stays and prescription medications. Setting: Saskatchewan, Canada. Patients: a total of 5762 women aged 55 years or more who took HT sometime between 1990 and 1997 and 5762 demographically matched controls who did not take HT from 1990 to 1997. Main outcome measures: total medical care expenditures and apparent costs of managing adverse events associated with HT.

Results: Excluding drug acquisition costs for HT and costs of care for osteoporosis, women in their first year of postmenopausal HT had total medical care costs about $400 greater than women who had never used HT (1997 Canadian dollars). This total medical care cost differential falls to about $90 to $120 per annum after the first year of therapy. If osteoporosis-related medical care costs are not excluded, the cost differential is about $390 during the first year of therapy and $80 to $110 per annum after the first year of therapy. These excess costs primarily are the result of excess rates of resource utilization for uterine- and breast-related diagnostic and treatment procedures.

Conclusion: Medical management costs for HT may be substantial during the first year of therapy, and some medical management costs may persist over several years. These short-term management costs, combined with recent data about the long-term safety of HT as a preventive therapy, reinforce the importance of considering therapeutic alternatives to HT.

Keywords: costs, hormone, postmenopausal, therapy.

Introduction

Estrogen plus progestogen hormone therapy (HT) is used for the symptomatic treatment of menopause and often has been used for the prevention of postmenopausal osteoporosis. Rates of use have varied substantially over time as perceptions have changed about the relative benefits and risks of HT. After the discovery in the 1980s that the addition of a progestogen to estrogen therapy (ET) decreased the risk of endometrial cancer, HT use steadily increased. By 1995, more than half of all postmenopausal women in the United States had used either ET or HT at least once [1–3].

However, recent data from the HT portion of the Women's Health Initiative (WHI) randomized trial question the clinical value of HT as a long-term preventive therapy [4]. Specifically, although use of HT over a 5-year period was associated with a reduction in the risk of osteoporotic fractures and colorectal cancer, HT use also was associated with an increase in the risk of coronary heart disease (CHD) events, stroke, breast cancer, and deep vein thrombosis/pulmonary embolism (DVT/PE). For otherwise healthy women, the overall risks of HT were judged to outweigh the benefits of HT as a long-term preventive therapy [5]. The implications of the WHI findings for HT as a short-term treatment for menopausal symptoms are less clear.

Although studies such as WHI have shed light on the incidence of serious adverse effects of HT, little is known about the levels of medical care resources associated with the management of these events, or any costs associated with the management of more common minor adverse events of HT (e.g., abnormal uterine bleeding, breast discomfort). More gen-

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erally, little is known about overall medical care resource utilization and costs among HT users relative to nonusers after initiation of HT.

This study helps fill these gaps by providing a comparative analysis of medical care costs among postmenopausal women in Saskatchewan, Canada over an 8-year period from 1990 to 1997. We estimate the net costs of HT use in a retrospective population-based study of HT users and nonusers. For simplicity, we focus on women who were potential candidates for combined estrogen–progestogen treatment (i.e., postmenopausal women with an intact uterus). The impact of the duration of HT use also is assessed.

Background

Medical Management of HT

As with virtually all prescription drugs, there are adverse events associated with HT use. Rare but serious adverse events include DVT/PE, CHD events and stroke. Less serious but more common adverse events (or "side effects") include irregular or abnormal vaginal or uterine bleeding, breast pain, and increased breast nodularity. Serious but relatively rare adverse events may have a significant impact on the costs associated with therapy from a population perspective if the cost per serious adverse event is substantial. Minor adverse events also can have a significant impact on the cost of therapy from a population perspective if these events are common and the cost per event is not small.

Several studies also have shown significant increased need for gynecologic procedures for evaluation among HT users compared to nonusers. In retrospective case–control studies, Ettinger and colleagues found that the incidence of abnormal vaginal bleeding requiring gynecologic procedures for evaluation, such as endometrial biopsy, were higher among HT users compared to nonusers, both for women using cyclic progestogen-estrogen replacement therapy [6] and continuous combined estrogen–progestogen therapy [7]. In another study, a significant percentage of physicians (16%) in Washington, Alaska, Montana, and Idaho reported routinely using endometrial biopsies to monitor patients receiving HT [8]. In a companion study to the present study, Thorp et al. [9] found new HT users were more likely to receive an endometrial biopsy or a dilation and curettage procedure over the first 1 to 3 years of therapy. Results from these retrospective and observational studies were confirmed in the WHI trial [10]. Among women not scheduled for routine endometrial biopsy as part of the study protocol, 33% of those assigned to HT had an endometrial biopsy, compared to 6% in the placebo group ($P < 0.001$). Of these, 38% (13% overall) had more than one biopsy in the HT group, compared to 16% (1% overall) in the placebo group.

The absolute increase in breast cancer risk found in WHI is small and similar to that found in observational studies of HT users [11–13]. Nonetheless, the potential for increased breast cancer risk coupled with increased breast symptoms may prompt additional evaluation and lead to increased use of mammograms among HT users. In addition, studies have shown HT to reduce both the specificity and sensitivity of mammograms [14,15]. This greater uncertainty may lead to a greater number of supplemental diagnostic tests and lower screening effectiveness. For example, Thorp et al. [9] found new HT users were more likely to receive a breast biopsy during the first 2 years of therapy. These findings have been confirmed by the WHI trial [16]—women assigned to the HT group were more likely to have abnormal mammography findings resulting in additional evaluation than women assigned to placebo during every year of therapy ($P < 0.001$).

In addition to costs associated with diagnostic procedures, minor adverse events also may contribute to costs if women experiencing these problems return to their physician to obtain a new HT prescription with a different active ingredient, strength, administration form or regimen. Recent studies have found that almost one-third of HT users switched regimens, dosages or administration type during an initial episode of use [2,17,18]. These additional visits and prescriptions add to the costs of managing HT.

The medical costs associated with managing HT use must be considered against medical costs averted due to the clinical benefits of HT. These benefits historically have been presumed to include, among others, a reduced incidence of osteoporotic fractures and a reduced risk for CHD events. However, the recent WHI trial results confirm earlier findings of an increase CHD risk, at least early in the course of HT [19–22]. If HT increases the risk of CHD events during the first year, short-term cost could increase among HT users as a population, even if such cases are relatively rare.

Some of the medical management costs may be offset by the cost of events avoided as a consequence of HT. For example, estimated total annual medical care treatment costs among women 45 and

older in the United States were almost $13 billion for osteoporosis [23]. If HT is effective in preventing osteoporotic fractures, some of the substantial costs of treating these fractures may be averted among the population of HT users.

Design

Materials and Methods

Saskatchewan Health (SH) funds universal coverage of a wide range of health services to its population of about one million people. Information on health service use is kept centrally in several linkable computerized data files [24]. The Saskatchewan administrative databases include a health insurance registration file, a cancer registry, and files with outpatient prescription drugs, hospital services and physician services data. We drew data from each of these files for a set of women meeting our inclusion criteria.

Inclusion criteria. We included postmenopausal women with an intact uterus who were taking HT primarily for its long-term prevention benefits and an equal number of postmenopausal women with an intact uterus who had no medical contraindications to HT but did not use HT during the study period. The study population was restricted to women aged 55 years and over to exclude women who took HT primarily for the alleviation of symptoms during perimenopause. We included women who were 55 by January 1, 1990, as well as women turning 55 between January 1, 1990 and December 31, 1994. However, we only included the woman's HT experience after her 55th birthday.

We also excluded women who had hospitalizations for a hysterectomy, thrombophlebitis, or a thromboembolic disorder between 1970 and 1990 and women recorded in the cancer registry with a diagnosis of breast cancer or uterine cancer between 1967 and 1990. These conditions often were considered contraindications to HT use. In addition, because of incomplete data, we excluded women residing in long-term care facilities, women whose prescriptions were paid by a government agency other than SH, and women with less than 4 years of coverage under SH (1 year before taking HT and 3 years after initiation of HT).

Definition of HT user. We identified an eligible woman as an HT user if she had at least one prescription filled from January 1, 1990 through December 31, 1994 for: 1) a progestogen (medroxyprogesterone acetate, micronized progesterone, norethindrone, or other progestogen-only oral contraceptive) plus at least one estrogen (chlorotrianisene, estradiol, conjugated estrogen, diethylstilbestrol, estropipate, ethinyl estrodial) within 90 days of the progestogen prescription; 2) a combination estrogen–progestogen transdermal treatment (Estracomb); or 3) an oral contraceptive. Women whose only estrogen prescription was for a vaginal estrogen cream or whose only progestogen prescription was for an injectable progestogen did not qualify as HT users.

A total of 77,278 women met our inclusion criteria. Of these women, 5726 women, or 7.4%, met our definition of HT users. Because the oldest HT user was 85 years of age by January 1, 1990, we used this as an age cut-off for defining the population of potential users in Saskatchewan.

Definition of non-HT users. An equal number of women who "never" used HT between January 1989 and December 1997 were matched to the users based on age, marital status, and residence in a large city, small city or rural area. The comparison group women had to match exactly with HT users on marital status (married or not married) and residence, but could be 1 year older or younger than the HT user. In addition, comparison group women had to meet the same criteria on contraindications, residence in long-term care facilities, and SH coverage as did HT users. The matching HT user's index prescription date was used as the date for ensuring adequate follow-up among the never users.

For the analyses below, we summarized the data for each woman into person-year summary records for the calendar years from 1990 to 1997. We included only women who were aged 55 years or more during the analysis year and who remained alive and covered by SH for the entire year. Thus, the sample size varies by year, increasing from 1990 to 1994 as new women aged into the study and declining slightly in the latter 3 years from loss to follow-up. Because we wanted at least 3 years of follow-up data, no new 55-year olds were added to the study population from 1995 to 1997.

Measurement of HT use. We broke out HT users by duration of HT use in the prior 2 years: 1) women who had less than a full year of HT use in the current year and no use in the preceding year were designated as users with less than 1 year of continuous HT use; 2) women who had used HT for the full 12 months of the current year but only part of the preceding year were designated to have had 1 to 2 years of continuous HT use; 3) women who had a full 12 months of HT use in the current year and in the prior year were designated to have

had more than 2 years of continuous HT use; and 4) women who had discontinuous use in the preceding 2 years or had used HT only during other years of the study period were designated as "other users."

Measures of resource use. Costs were estimated by payments made by SH to providers of care. Nevertheless, whereas the prescription and physician service records in the SH database contain the payment amounts, the hospital records had only a resource intensity weight (RIW). The cost of a given hospitalization from 1992 to 1997 was computed by multiplying the RIW by the estimated cost per weighted case. The estimated cost per weighted case was calculated by SH based on the available acute care funding, minus funding related to emergency room services and outpatient clinics, for a given year divided by the total number of weighted cases for that year. In 1996/97, the estimated cost per weighted case was approximately $2,000. For hospitalizations before 1992, a weighted average per diem rate of $341 (in 1996/97 Canadian dollars) was multiplied by the length of stay in days to estimate short-term hospital costs. Current year physician service and prescription medication payments were multiplied by the health-care component of the Canadian Consumer Price Index to obtain constant 1997 dollars.

Total costs were computed by summing aggregated costs for physician services, prescription medications and hospital care. Although these services are the largest components of health-care costs, they are missing some important resources. For instance, the data file does not include radiology services conducted at independent radiology centers. Because HT use causes increased risk of breast pain and nodularity that could prompt additional mammogram use, our estimates of medical management costs for HT could be underestimated and should be considered conservative.

Finally, where Canadian dollars were converted to US equivalent dollars, we multiplied the expenditure figures by the the Organization for Economic Cooperation and Development's (OECD) 1996 purchasing power parity for Canada divided by that of the United States—a ratio of $1 Canadian to $0.77 US [25].

Analytic Methods

We conducted a multivariate analysis of total annual medical expenditures 1) excluding expenditures for HT and lipid-lowering medications; and 2) excluding expenditures for HT, lipid-lowering medications, and osteoporosis treatment. Our goal for the multivariate analysis was twofold: 1) to control for any differences in the population that may affect total medical care resource use other than the use of HT; and 2) to identify expenditures for medical management of HT net of any savings for HT from treatment costs averted.

HT users may be either healthier or less healthy on average than women not taking HT. To control for potential selection bias, we included several prior year health status variables in the multivariate equations. These are total medical care resources consumed in the prior year and indicators for whether the woman had medical care contacts for osteoporosis, CHD and menopausal disorders in the prior year.

For robust variance estimates, we used a fixed-effect model and the general estimating equation (GEE) method which accounts for both heteroskedasticity of the variances (i.e., unequal variances) and the intercluster correlation of repeated measures on the same subject. Further, because the distribution of total medical care costs was skewed to the right, we ran the regressions on the natural logarithm of total medical costs. The logarithmic specification gives less weight to very large costs. We also dropped four high-cost outliers; three never users with total costs of $123,143, $98,303, and $83,318, respectively, and one current nonuser with total costs of $99,971 were dropped. Women with conditions requiring such high medical costs in a single year would not be candidates for preventive HT and therefore their exclusion is not believed to bias our results.

Predicted medical management costs. Cost differentials between HT users and nonusers could result from differences in drug costs, any costs of medical management of HT (dose titration, monitoring and treating side effects), and treatment costs averted due to the clinical benefits of HT. The drug costs of HT were easily identified and subtracted out from the total cost for HT users before estimating the cost model. At the time of the study, HT was often used as a lipid-lowering drug among postmenopausal women, so the costs of all lipid-lowering medications also were identified and subtracted from total expenditures for both HT users and never users. An alternative cost metric further subtracted out costs associated with osteoporosis treatment. However, the cost of treatment for osteoporosis was not as easily identifiable in the database as were drug costs; records with diagnostic codes for osteoporosis may not include

all related costs. Therefore, we computed these costs from the estimated coefficients for binary (dummy) variables for any current-year medical care for osteoporosis. Because we expected the costs to vary by duration of HT use, we also included interaction terms for osteoporosis treatment and four HT user categories.

We estimated total costs for each HT user group and for never users first assuming the average prevalence of osteoporosis among the study population. The differences in total costs between the user groups and never users were then computed from these totals. These differences are the apparent medical management costs of HT net of any current-year cost impact of HT on osteoporosis treatment costs. We then recomputed medical management costs first for women without osteoporosis care in the current year by setting the indicators for osteoporosis to zero. Using these estimates, we similarly found the differences in total costs between the user groups and never users. Predicted logarithms of total and medical management costs were converted to dollars by using HT-user-group-specific error retransformation factors, computed as the average exponential of the residuals.

As noted by Manning [26], retransforming the expectation of a logged variable back into natural units is complicated by heteroskedasticity. For this reason, we used the HT-user-group-specific smearing factors to account for the heteroskedasticity in our sample. Another method, suggested by Mullahy [27], involves estimating the relationship using an exponential conditional mean (ECM) regression model. To investigate the sensitivity of our results to our choice of smearing factors, we estimated our equations using ECM methods. All results were qualitatively similar to the logarithmic cost results.

Results

Characteristics of the Study Population

Selected statistics on the demographic and health characteristics of the study women are provided in Table 1. Prior year health characteristics were measured in the 12 months preceding a user's first purchase of a progestogen or estrogen prescription after her 55th birthday. For nonusers, the prescription purchase date of their matching user was used.

The average age of the study population as of January 1990 was 57.2 years; more than 71% were married; and 42% lived in one of Saskatchewan's two largest cities (Regina and Saskatoon), 17.5% lived in the province's smaller cities, and the remaining 40.5% lived in rural areas. Users were more likely to have used health-care services than nonusers: they had significantly more physician visits in a 12-month period, were significantly more likely to be hospitalized in that time, and had significantly higher total annual medical costs. Based on hospital and physician service records, users were more likely than nonusers to have had osteoporosis but were equally likely to have had CHD.

Multivariate Analysis of Total Annual Medical Costs

Of the 82,020 person-years of data for women aged 55 years and over from 1990 through 1997, a total of 4772 records were dropped because of the lack of prior year data, leaving 77,248 person-years for the analysis of all women. The estimated GEE coefficients for the logarithm of total medical resource use are shown in Table 2. They should be read as the percentage change in total medical resources given a change in the associated explanatory variable.

The estimated coefficients of the variables for current HT users are positive and statistically

Table 1 Demographic and health characteristics of HT users and nonusers in Saskatchewan Canada, 1990 to 1994

	Users	Nonusers
Number	5762	5762
Matching characteristics		
Mean age in years (standard deviation)	57.2 (6.0)	57.2 (6.0)
Percent married	71.4%	71.4%
Percent residing in large cities	42.0%	42.0%
Percent residing in small cities	17.5%	17.5%
Health-care resource use in prior year†		
Percent hospitalized	5.4%*	3.7%
Mean number of physician visits, prior year (SD)	14.1 (12.5)*	9.2 (11.0)
Total medical costs‡ in prior year (SD)	$1157 ($1876)*	$857 ($2319)
Percent with physician visit(s) in year before first HT prescription at age 55+† for		
Osteoporosis	7.3%*	3.0%
Coronary heart disease	21.1%	20.9%

*Significantly different from the estimate for nonusers at the $P < 0.001$ level.
†For nonusers, the prescription purchase date of their matching user was used to determine the "prior year."
‡Total medical costs here include costs for only physician services, prescription medications and short-term hospital stays.

Table 2 General estimating equation coefficients (standard errors) for total annual medical care costs excluding costs for HT and lipid-lowering medications

	Coefficients	Standard errors
Intercept	2.94*	(0.151)
Current HT user with <1 year continuous use (Never user omitted)	1.56*	(0.039)
Current HT user with 1–2 year continuous use	1.20*	(0.046)
Current HT user with >2 year continuous use	1.17*	(0.033)
Other HT user (e.g., with discontinuous use)	0.98*	(0.028)
Age	0.03*	(0.002)
Resides in large city (rural omitted)	0.15*	(0.028)
Resides in small city	0.02	(0.036)
Married	–0.15*	(0.029)
Medical care for CHD in prior year	0.32*	(0.017)
Medical care for CHD this year	1.37*	(0.024)
Current HT user with <1 year use	–1.01*	(0.062)
Current HT user with 1–2 year use	–0.80*	(0.081)
Current HT user with >2 year use	–0.86*	(0.045)
Other HT user	–0.61*	(0.035)
Medical care for osteoporosis in prior year	0.11†	(0.037)
Medical care for osteoporosis this year	0.85*	(0.066)
Current HT user with <1 year use	–0.50*	(0.106)
Current HT user with 1–2 year use	–0.51†	(0.163)
Current HT user with >2 year use	–0.59*	(0.105)
Other HT user	–0.31*	(0.084)
Medical care for menopausal disorders in prior year	0.12*	(0.017)
Total medical costs in prior year (measured as percentage of average)	0.07*	(0.003)
1990 (1997 omitted)	0.20*	(0.026)
1991	0.18*	(0.024)
1992	0.07*	(0.022)
1993	–0.09*	(0.021)
1994	–0.19*	(0.020)
1995	–0.17*	(0.019)
1996	–0.04†	(0.018)
Number of person-years	77,248	

*$P < 0.01$.
†$P < 0.05$.

significant ($P < 0.001$), with current HT users having the largest coefficient. The coefficients for current HT users with 1 to 2 years and users with more than 2 years of use are roughly equivalent in magnitude.

The coefficient for osteoporosis-related medical care in the current year is positive and statistically significant ($P < 0.05$). The interaction terms between this variable and the current use indicators are all negative and statistically significant ($P < 0.001$), suggesting that HT users with current year osteoporosis-related medical care use had lower medical care costs for osteoporosis than never users.

Several other covariates had statistically significant estimated coefficients in the model. Women with higher total medical care costs in the prior year had significantly higher medical resource use in the current year ($P < 0.001$). Current year medical expenditures were higher among women with prior year expenditures for osteoporosis ($P < 0.05$) or CHD ($P < 0.001$). The coefficient for a diagnosis of menopausal disorders in the prior year is also statistically significant ($P < 0.001$) but is relatively small in magnitude. This may be a result of the lack of specificity in this variable; because the SH physician services file only had three-digit ICD-9 (International Classification of Diseases, ninth revision) codes, we could not distinguish hypestrogenic (e.g., hot flashes) conditions requiring little medical intervention and monitoring from hyperestrogenic (e.g., vaginal bleeding) conditions potentially requiring significant intervention and monitoring. The coefficient for the current year CHD medical care use variable is positive and statistically significant ($P < 0.001$), and the interaction terms with the HT user variables are negative and statistically significant ($P < 0.001$).

Total medical care expenditures also increased with age ($P < 0.001$), and married women had lower medical care costs compared to unmarried women ($P < 0.001$). The coefficient for residence in a large city is positive and statistically significant ($P < 0.001$), but the coefficient for residence in a small city is not statistically significant.

The coefficients of the year dummies are positive for 1990 to 1992 and negative for 1993 to 1996 (reference year 1997). As noted, due to availability of cost information in the administrative data, the methods used to estimate inpatient costs for 1990 to

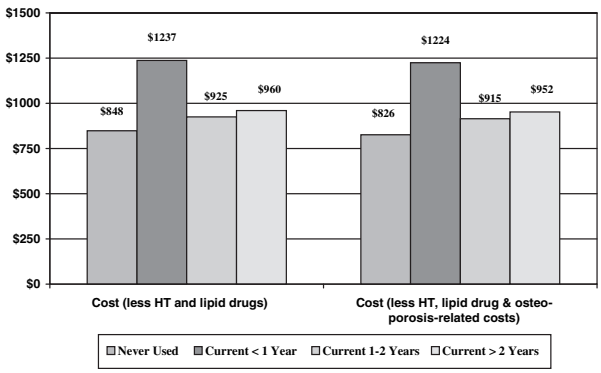

Figure 1 Estimated annual medical expenditures for current HT users and never users by duration of HT use (in 1997 Canadian dollars).

1992 differed from the methods used for 1993 to 1997. It is likely that the year dummy coefficients in part reflect this difference in costing methods over time.

Predicted Medical Management Costs

Predicted total medical care costs for HT users, by duration of therapy, and never users for the two measures of cost are shown in Fig. 1. Total medical care costs were higher for HT users than for never users, regardless of whether we included or excluded costs related to osteoporosis. In addition, total medical care costs were significantly higher for current users with less than 1 year of use compared to women with more than 1 year of continuous HT use. Using the average prevalence of osteoporosis-related care in the current year, we estimated medical care costs to total $1237 (in 1997 Canadian dollars) for women with new episodes of HT of under 1-year duration. Subtracting the estimated medical care costs for women who never used HT during the study period yields an estimate of medical care costs attributable to HT use. As reported in Table 3, the resulting attributable cost estimate is about $390 during the first year of HT use. This estimate reflects higher costs among HT users due to costs of medical management of HT adverse events net of any cost savings due to HT use. Of course, to estimate the total attributable costs of HT, annual costs of $100 to $200 (or $77 to $154 in US-equivalent dollars) for the HT medications must be restored to the estimated cost differentials.

However, the goal of the analysis is to estimate costs associated with HT adverse events (HT medical management costs). For this purpose, the cost of drug therapy and any cost savings resulting from the clinical benefits of HT should be excluded. As shown in Table 3, the attributable cost estimate increases to about $400 if the cost of osteoporosis care is excluded from both the HT-user and never-user groups. In other words, the difference between groups in osteoporosis treatment costs during the first year of therapy is on average about $10. Excluding this difference produces a more specific estimate of HT medical management costs potentially attributable to adverse events during the initial 12 months of treatment.

After the first year of HT, apparent medical management costs for HT declined substantially, but differences remained statistically significant. Excluding the costs of osteoporosis care from all groups, these costs were estimated to be in the range of $89 to $126 annually. If osteoporosis costs are not excluded, the estimated attributable costs of HT after the first year of therapy are about $77 to $112 annually.

Discussion

We investigated the level of medical care resources used by postmenopausal women with an intact uterus and no prior contraindications to combined estrogen–progestogen replacement treatment in Saskatchewan, Canada from 1990 through 1997. Different patterns of medical care resource use were found between HT users and nonusers and between HT users with less than 1 year of use and those with more than 1 year of continuous use. Because of the considerable costs for managing HT in the first year of use, annual medical care resource use was highest among women with new episodes of HT.

Excluding HT and lipid drug acquisition costs and excluding costs associated with treatment of osteoporosis, women in their first year of postmenopausal HT use had total medical care costs about

Table 3 Predicted annual medical care costs by duration of current HT use, 1997 Canadian dollars

Difference in costs between users and never users	Total costs less HT and lipid drug costs	Total costs less HT, lipid drug, and osteoporosis-related costs
Current HT users with <1 year of use	$389	$398
Current HT users with 1–2 years of use	$77	$89
Current HT users with >2 years of use	$112	$126

$400 greater than postmenopausal women who had not used HT, or about $308 in US-equivalent 1997 dollars. This total medical care cost differential falls to about $89 to $126 per annum after the first year of therapy ($69–97 in US-equivalent dollars). If potential osteoporosis-related cost offsets are not excluded, the costs differential is about $390, or $300 in US-equivalent dollars, during the first year of therapy and $80 to $110, or $62 to $85 in US-equivalent dollars, per annum after the first year. That is, first-year costs associated with managing adverse events were partially offset by osteoporosis-related costs that were $10 lower on average among HT users relative to nonusers.

The apparent decline in the cost of managing adverse events of HT with duration of therapy could reflect a tendency for some adverse events, such as abnormal bleeding, to occur less frequently after the first year of therapy. However, as noted, Chlebowski et al. [16] found higher rates of abnormal mammography results in the HT group compared to the placebo group in each year of the WHI study. Another possibility is that the reduction in costs associated with duration of HT results in part from differential rates of discontinuation of therapy among women. If those experiencing adverse effects of HT are more likely than others to discontinue therapy, women who remain on therapy will tend to be those with lower rates of adverse effects, and correspondingly lower costs.

Limitations

A significant limitation of this study is that women receiving HT may differ from non-HT users along a variety of characteristics that affect medical care costs. This limitation is common to any retrospective case–control analysis. We have used a variety of statistical adjustments for differences in observed characteristics across HT users and nonusers in an attempt to isolate the impact of HT on medical costs. In particular, we have controlled for both general patterns of medical care utilization before the initiation of HT as well as specific pre-existing comorbid conditions. A benefit of the "cradle to grave" health services coverage in the SH data, compared to a US administrative database, is that there is little attrition from the sample over time. As a result, we were able to exclude all women who had a hysterectomy or treatment for breast cancer over a 20-year period before the study index date. However, as with any analysis of administrative health data, some potentially relevant clinical characteristics of the women included in the analysis cannot be measured. Thus, our estimates of medical management costs may overstate these costs if women receiving HT also are more likely to use other services for reasons not accounted for in the analysis.

Dummy variables for current-year treatment for osteoporosis and CHD are used in the regression model, but these variables potentially are endogenous. Thus, their estimated coefficients could be biased. Attributable cost estimates excluding osteoporosis costs are most likely to be affected by this limitation, but the overall attributable cost estimates may be affected as well. An alternative approach would have been to construct an additional measure of "modified total" costs which excluded osteoporosis-related cost for both HT users and non-HT user controls as an alternative dependent variable in the regression model. However, as noted, some osteoporosis-related costs are not identifiable in the database through diagnosis or treatment codes. Thus, a modified cost measure excluding identifiable osteoporosis-related costs would not provide a complete exclusion of osteoporosis-related costs.

Another potential limitation of the analysis is the focus on differences in modified total health-care costs between HT users and matched nonusers. This method is based on the assumption that any difference in modified total costs, after controlling for other factors, is potentially attributable to HT. A more restrictive alternative is to only compare costs for specific procedures deemed likely to be related to evaluation or treatment for adverse events of HT. In addition, estimates of the attributable cost of HT during the first and subsequent years of therapy are obtained indirectly from synthetic cohorts based on coefficients of the categorical variables relating to patterns of HT use in the regression model for calendar year modified total cost data. This method follows that often used in prospective cohort studies, but an alternative would have been to identify "new" episodes of HT use based on the date of an initial HT prescription, and construct parallel episodes for each of the non-HT user controls based on a matching pseudo-index date.

A related study [28; Ohsfeldt RL, Chawla A, White LA, unpublished] provides a case–control analysis using US private insurance claims data for new episodes of HT use. The analysis focused on costs for a specific set of uterine- and breast-related evaluation and treatment procedures potentially related to HT use over a 2-year period after an index date for HT initiation for 902 new HT users and 2135 nonusers age 50 to 64. An exponential conditional mean regression model was used to estimate medical care expenditures for these proce-

dures over 2 years, controlling for observable factors such as baseline comorbidity factors and prior period medical care expenditures. The results indicated that costs for potentially HT-related procedures were $362 higher (in 1997 US$) for HT users compared to nonusers over the first 2 years of therapy. This estimate is remarkably similar to the medical management cost estimates for the SH data when expressed in US$ (i.e., $308 + $69 = $377).

While the similarities in these estimates (despite the differences in methods) are reassuring, given the limitations of both studies, additional research is needed to confirm or contradict the implications of our analysis. The usual solution to the patient treatment selection issue is to conduct a trial where patients are randomized to treatment or placebo groups. However, it would be difficult to design a randomized clinical trial to estimate medical management costs for HT in usual clinical practice. Nonetheless, at a minimum it would be useful to replicate this analysis using a large retrospective database that permits the extraction of potentially relevant clinical factors via access to patient medical records.

Concerns about long-term safety of HT are less relevant when considering HT as a short-term therapy for the relief of menopausal symptoms, such as severe hot flushes. Even in this context, the costs of managing adverse effects of therapy may be a relevant factor to balance against the well-established benefits of HT for menopausal symptom relief, especially if these costs during the first year of therapy are as great (or even greater) than HT drug costs. However, an additional limitation of our analysis is that it predates the advent of "low-dose" HT. To the extent low-dose HT generally is associated with lower adverse event rates than standard-dose HT, the costs of managing those adverse events probably would be lower as well. More data about the effectiveness and costs of low dose HT, as well as nonhormonal alternatives to HT, are needed to assess the benefits and costs of alternative treatments for menopausal symptoms.

Conclusion

Common minor adverse events that many women experience when taking HT may generate significant costs during the first year of therapy. These medical management costs appear to diminish among HT users over time but remain present for several years. Given concerns about the long-term safety of HT, current US Preventive Service Task Force [29] guidelines encourage clinicians to consider alternatives to HT for osteoporosis therapy, despite the benefits of HT for the prevention of osteoporosis. The apparent medical management cost for HT may provide yet another reason to consider alternative treatments for osteoporosis.

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