

# Changes in the Use of Postmenopausal Hormone Therapy after the Publication of Clinical Trial Results

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**Background:** The recent publication of clinical trial results has led to a dramatic shift in the evidence about postmenopausal hormone therapy.

**Objective:** To examine whether the publication of clinical trial results, specifically the Heart and Estrogen/progestin Replacement Study (HERS) in 1998 and the Women's Health Initiative (WHI) in 2002, has influenced the use of hormone therapy among postmenopausal women.

**Design:** Observational cohort (1997 to 2003).

**Setting:** San Francisco Mammography Registry, San Francisco, California.

**Participants:** Postmenopausal women between the ages of 50 and 74 years without a personal history of breast cancer who underwent mammography (151 862 mammograms).

**Measurements:** Self-reported current use of hormone therapy.

**Results:** Among menopausal women who had mammography, it was estimated that 41% were currently using hormone therapy in 1997. Before the publication of HERS, the use of hormone therapy

was increasing at a rate of 1% (95% CI, 0% to 2%) per quarter. After the publication of HERS, use decreased by 1% (CI, -3% to 0%) per quarter. In contrast, the publication of the WHI in 2002 was associated with a more substantial decline in the use of hormone therapy of 18% (CI, -21% to -16%) per quarter. Similar associations were observed for most subgroups of women, including women older than 65 years of age; women with a previous hysterectomy; and women who described their race or ethnicity as white, African American, Latina, Chinese, or Filipina.

**Conclusions:** The release of the HERS data was temporally associated with a modest decline in the use of hormone therapy. In contrast, the release of the principal findings from the WHI was associated with a more substantial decline in use by postmenopausal women. The reason for the differences in decline may relate to the fact that the WHI results were widely publicized or were more applicable to most postmenopausal women because the WHI study was performed in healthy women.

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In 1995, approximately 38% of postmenopausal women in the United States were taking hormone therapy (1). At that time, several observational studies had suggested that hormone therapy offered women some protection against coronary heart disease and osteoporosis (2-5). A decision analysis published in 1997 concluded that the benefits of hormone therapy outweighed its risks for nearly all women (6). More recently, the results from 2 large randomized clinical trials, the Heart and Estrogen/progestin Replacement Study (HERS) (7) and the Women's Health Initiative (WHI), have been published (8). These clinical trials demonstrated that the risks associated with hormone therapy outweigh the benefits for women taking continuous estrogen and progestin regimens. As a result of these trial results, the U.S. Food and Drug Administration required new warning labels for all estrogen products (9), and the U.S. Preventive Services Task Force revised its assessment of hormone therapy to recommend against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women (10).

It is important to understand whether this new scientific evidence is changing the use of hormone therapy. Of note, the results of the WHI were widely disseminated. Despite this publicity, differential access to new information, varied interpretations of study findings, and individual perceptions of menopausal symptoms and hormone side effects may have resulted in different patterns of use. An understanding of how use is changing over time pro-

vides important information about the dissemination of clinical trial results to women.

We designed our analysis to examine whether the use of hormone therapy has changed among postmenopausal women as a result of the publication of the results from HERS and the WHI. We were also interested in examining whether patterns of use differ by patient characteristics. Because HERS examined the outcomes of older women, we hypothesized that there would be earlier and more substantial declines in hormone therapy use among this group. We also expected that there would be variation in use by race or ethnicity because white women may have better access to new information (11). Finally, because the WHI study results were specific to women taking continuous estrogen plus progestin, we hypothesized that hormone use would be more stable among women who had had hysterectomies because such women typically take only estrogen and may believe that the findings do not apply to them.

## METHODS

### Sample

The San Francisco Mammography Registry is a population-based registry of women undergoing mammography in San Francisco, California. It is 1 of 7 registries participating in the National Cancer Institute Breast Cancer Surveillance Consortium (12). This registry began to prospectively collect patient data and mammography re-

sults in 1995 and currently captures about 90% of mammography examinations performed in San Francisco. Data from 11 mammography facilities are included in this analysis. Women were eligible for this analysis if they were between the ages of 50 to 74 years, were postmenopausal, did not report a personal history of breast cancer, and underwent screening or diagnostic mammography between January 1997 and 19 May 2003. Women 55 years of age and older were assumed to be menopausal. Women 50 to 54 years of age were considered to be menopausal if both ovaries had been removed or if they reported that their periods had stopped permanently. For women who had mammography more than once in any calendar year, we included only the first instance of mammography in that year to prevent overrepresentation of women undergoing an evaluation of an abnormal mammogram because this experience may influence use of hormone therapy. Our final sample included 151 862 mammograms received by 71 219 women.

### Data

At the facilities that participate in the San Francisco Mammography Registry, each woman completes a brief, scannable questionnaire at the time of mammography. This questionnaire collects information about current use of hormone therapy and several personal characteristics, including race or ethnicity (categorized as white, African American, Latina, Chinese, Filipina, other Asian, other), family history of breast cancer (including mother, sisters, and daughters), history of childbirth, whether the woman had undergone a hysterectomy, menopausal status, history of breast biopsy (including fine-needle aspiration, core biopsy, and surgical biopsy). Information about age at the time of mammography, date of mammography, and ZIP code of residence is reported by the facility. Data from the year 2000 U.S. Census was used to assign median income for each woman's ZIP code of residence as a proxy for socioeconomic status.

### Variables

Our outcome variable for this analysis was the current use of hormone therapy. Date of mammography was represented as a linear term. Binary variables were created for the publication dates of HERS (before 19 August 1998 vs. that date or later) and the publication of the principal findings from the WHI (before 17 July 2002 vs. that date or later). Other independent variables examined were age at the time of mammography, race or ethnicity, median income of the ZIP code of residence, history of childbirth, family history of breast cancer, history of breast biopsy, and previous hysterectomy.

### Statistical Analysis

Because some of the women in this sample had more than 1 mammogram represented in this data set, which spanned a 7-year period, we conducted a repeated-measures logistic regression to adjust the variance estimates for clustering of hormone therapy use over time for individual

### Context

Since 1998, 2 large trials have drastically changed the evidence for the preventive health benefits of postmenopausal hormone replacement therapy. However, changes in practice often lag behind changes in evidence.

### Contribution

Among mammography recipients in San Francisco, California, the use of hormone replacement therapy decreased 1% per quarter after publication of the Heart and Estrogen/progestin Replacement Study and 18% per quarter after publication of results from the Women's Health Initiative (WHI). Reduction in use was unrelated to a woman's age, hysterectomy status, or race or ethnicity.

### Implications

The WHI resulted in more dramatic changes in practice than are often associated with changes in evidence. The vigorous media coverage of the WHI may have contributed to rapid changes in practice.

—The Editors

women and for the clustering of women within mammography facilities (13). Generalized estimating equations were implemented by using the SUDAAN statistical package, version 8.0.0 (Research Triangle Institute, Research Triangle Park, North Carolina) assuming an exchangeable correlation matrix. These models included a linear term indicating quarter from January 1997 to the first quarter of 2003 to control for temporal trends (the last quarter included mammograms through 19 May 2003), the variables specified above to indicate the dates of publication of HERS and the WHI, and an interaction term between each of these publication indicators and the time (in quarters) following each of these publications to measure changes in use after the publication of these clinical trials. These models also controlled for the individual characteristics described earlier (that is, age, race or ethnicity, history of childbirth, family history of breast cancer, history of breast biopsy, previous hysterectomy, median income for the ZIP code of residence). To specifically test our hypotheses about differential changes in the use of hormone therapy for subgroups of women on the basis of age, hysterectomy status, and race or ethnicity, we examined interaction terms to test for effect modification. For the main effects, a *P* value less than 0.05 was considered statistically significant, and for the interaction terms, a *P* value less than 0.01 was considered to be statistically significant. The likelihood ratio test compared the null model with the fitted model.

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Table. Description of the Sample (151 862 Mammograms)\*

Characteristic	Year						
	1997	1998	1999	2000	2001	2002	2003†
Mammograms, <i>n</i>	14 051	21 934	23 934	24 842	27 555	29 877	9669
Median age, <i>y</i>	61	60	60	60	59	59	59
Race and ethnicity, %							
White	49.2	52.9	54.5	53.9	51.6	47.9	48.9
African American	11.3	9.5	8.6	8.2	8.3	8.3	8.9
Latina	14.0	11.3	11.0	10.7	11.0	11.8	12.2
Chinese	11.3	13.3	13.3	15.0	16.0	18.6	16.3
Filipina	8.5	7.0	6.7	6.7	7.3	7.8	8.0
Other Asian	4.7	5.2	5.0	4.8	5.2	5.0	4.8
Other	1.0	0.8	0.9	0.7	0.6	0.6	0.9
History of childbirth, %	75.2	72.6	71.6	71.3	71.6	72.2	71.7
Family history of breast cancer, %	11.8	13.6	14.6	15.8	16.0	15.8	17.1
History of breast biopsy, %	21.8	23.6	24.5	25.1	26.0	26.3	27.6
Previous hysterectomy, %	26.6	26.1	26.2	24.6	24.4	23.2	23.6

\* Trend across years is significant at  $P < 0.001$  for all variables except the percentage of whites, the percentage of Latinas, the percentage of other race and ethnicity, history of childbirth, and median income. Data were missing for race and ethnicity ( $n = 7273$ ), income ( $n = 1242$ ), history of childbirth ( $n = 3792$ ), family history of breast cancer ( $n = 5162$ ), history of breast biopsy or aspiration ( $n = 1797$ ), and previous hysterectomy ( $n = 5333$ ).

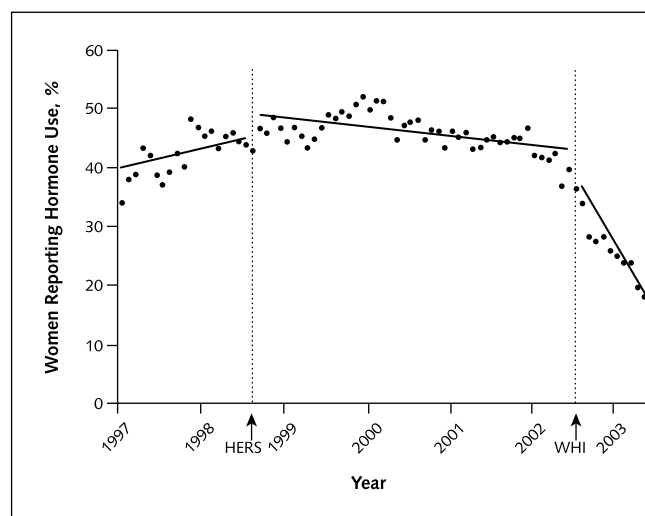
† Represents data collected from 1 January through 19 May 2003.

## RESULTS

The Table shows the characteristics of the sample for each of the study years. Over the time period of the study, the median age decreased from 61 years to 59 years. The racial and ethnic composition of the sample also changed somewhat across the study years. Fewer women undergo-

ing mammography in 2003 reported a history of childbirth (71.7% vs. 75.2%) or hysterectomy than did women undergoing mammography in 1997. Conversely, more women reported a family history of breast cancer (17.1% vs. 11.8%) or a personal history of a previous breast biopsy or aspiration. The average number of mammograms obtained for each woman in our sample across the 7-year study period was 2.1 (range, 1 to 7).

Figure. Rates of hormone therapy use among postmenopausal women, 1997 to 2003.



The first vertical line represents the publication date of the Heart and Estrogen/progestin Replacement Study (HERS) in August 1998. The second vertical line represents the publication date of the Women's Health Initiative (WHI) in July 2002. Circles represent unadjusted rates of current hormone therapy use for each month between January 1997 and May 2003. Lines represent the adjusted change in hormone therapy use for 3 time periods: before the publication of HERS, after the publication of HERS, and before and after the publication of the WHI. Change in hormone therapy use is adjusted for age, race or ethnicity, history of childbirth, family history of breast cancer, history of breast biopsy, previous hysterectomy, and median income for the ZIP code of residence.

The Figure shows the unadjusted rates of current hormone therapy use by month for all of the women in the sample. Among menopausal women who had received mammography, we estimated that the average proportion reporting the current use of hormone therapy was 41% in 1997. In 1997, hormone use was highest among white women (52.6%) and lowest among African-American women (34.1%), Latina women (33.9%), Chinese women (32.2%), and Filipina women (29.6%). In 1997, hormone use was higher among younger women than older women (48.7% vs. 28.7%;  $P < 0.001$ ) and among women who had had a hysterectomy compared with women who had not had a hysterectomy (60.0% vs. 36.4%;  $P < 0.001$ ).

The adjusted multivariate model estimates that before the publication of HERS, the use of hormone therapy was increasing at a rate of 1% (CI, 0% to 2%) per quarter. Following the publication of HERS, there was a decrease in use of 1% (CI, -3% to 0%) per quarter. In contrast, the publication of the WHI was associated with a decline in use of 18% (CI, -21% to -16%) per quarter. Similar associations were observed for all of the subgroups of women examined. The Figure shows these adjusted trends.

## DISCUSSION

The past several years have witnessed a dramatic shift in the evidence on the use of hormone therapy by menopausal women. Our study suggests that the release of data

from HERS was associated with a modest decline in the use of hormone therapy, whereas the release of the principal findings from the WHI was associated with a more substantial decline in use. Similar associations were observed for all of the subgroups of women examined.

The results from HERS may have had a modest association with the use of hormone therapy because this trial included only women with documented coronary heart disease (7). At the time of publication, this study may have been greeted with more skepticism because it was the first clinical trial to contradict the findings of several observational studies (2–5). Even the HERS investigators were cautious in concluding that while they “[did] not recommend starting this treatment for the purpose of secondary prevention of coronary heart disease . . . it could be appropriate for women already receiving this treatment to continue” (7). Although we cannot examine the effect of HERS on the behavior of women with coronary heart disease, we did examine the larger group of women older than 65 years of age and found that use did not differ statistically from use in younger women.

Why was there a more substantial change in the use of hormone therapy in response to the WHI? Although our data cannot directly address this issue, several explanations are possible. Of note, the findings from the WHI were widely publicized and apply to healthy postmenopausal women. Second, HERS was conducted for the full study time period. In comparison, the WHI was stopped prematurely by the data safety monitoring board. Third, the dissemination of new evidence may be cumulative, particularly when the evidence conflicts with current practices (14). Fourth, in contrast to the HERS investigators, the WHI investigators were more decisive in concluding that “this regimen should not be initiated or continued for primary prevention of coronary heart disease” (8).

Although the WHI findings apply to women taking continuous estrogen and progestin regimens, we found no statistical evidence that the decline in use differed among women who have had a hysterectomy, a group that typically takes unopposed estrogen. Because our sample is large and ethnically diverse, we examined the patterns of use in several racial and ethnic groups. Of note, our study also found no statistical evidence that the observed decline in hormone therapy use differed by race or ethnicity among the groups examined.

Although our data were limited to San Francisco, our baseline rates of hormone therapy use are similar to those described in a national household survey (1). Because our sample was derived from a mammography registry, our findings may not be generalizable to women who have not had mammography. However, recent data suggest that approximately 80% of women from 50 to 64 years of age have had a mammogram within 2 years (15). Our data do not include information about the specific type of hormone therapy taken. At the time of this analysis, data are available only for the 10 months after the publication of

the WHI. Longer follow-up may be necessary to attain stable changes in practice patterns after the publication of a clinical trial (16). Despite these limitations, this large, population-based sample provides a reliable estimate of hormone therapy use over this time period.

In summary, the publication of HERS was temporally associated with a modest decline in the use of hormone therapy by postmenopausal women, whereas the release of the principal findings from the WHI was associated with a substantial decline in use. Substantial declines in hormone therapy use were seen for most subgroups of women, including women with a previous hysterectomy, women older than 65 years of age, and women from several racial or ethnic groups. Additional research should consider which factors lead to the effective dissemination of new clinical trial findings for women.

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