Decline in use of hormone therapy among postmenopausal women in the United Kingdom

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Abstract

Objective: There has been controversy about the results of the Women’s Health Initiative and the Million Women Study and uncertainty about their impact on hormone therapy (HT) use. This study documents recent trends in HT use in postmenopausal women in the United Kingdom.

Design: Between April 2001 and September 2005, 202,638 postmenopausal women aged 50 to 74 and with no history of bilateral oophorectomy were recruited to the United Kingdom Collaborative Trial of Ovarian Cancer Screening. The proportion of women randomized each month who were using HT was calculated. The trend in HT use was assessed with reference to the publication of the Women’s Health Initiative interim results (July 2002), the Million Women Study (August 2003), and advice from the UK Committee on Safety of Medicines (December 2003).

Results: The median number of women recruited and randomized per month was 3,955 (mean 3,744). The proportion of randomized women using HT between April 2001 and June 2002 was 29%. This was followed by a steady monthly decline, and by February to September 2005, only 10% to 11% of newly recruited women were using HT. This trend was present in all age groups. However, in current users, the average duration of HT use remained steady at 10 to 11 years.

Conclusions: There was a steady decline in HT use among postmenopausal women at recruitment into the United Kingdom Collaborative Trial of Ovarian Cancer Screening between April 2001 and September 2005. This is likely to reflect general trends in the UK population and is probably related to the premature closure of the large HT trials and the ensuing publicity.

Key Words: Hormone therapy – Change in use – United Kingdom – United Kingdom Collaborative Trial of Ovarian Cancer Screening – UKCTOCS.

In the past two decades, there have been marked changes in the recommendations and uptake of hormone therapy (HT). In 1990, 10% of women aged 50 to 64 years used HT.1 After observational studies showing significant benefits in the treatment of menopausal symptoms and reduction in the incidence of osteoporosis, cardiovascular disease, Alzheimer’s disease, depression, stroke, and colon cancer,2-5 this figure rose steadily to 30% in 1995.6

In the late 1990s, large randomized, controlled trials in the United States (Women’s Health Initiative [WHI]) and observational studies in the United Kingdom (Million Women Study [MWS]) were instituted to confirm the findings of the smaller studies. The estrogen and progesterone arm of the WHI study was terminated prematurely in May 2002 due to the reported increase in the risk of breast cancer, coronary heart disease, stroke, and pulmonary embolism. These risks were thought to outweigh any benefits from reduced risks of osteoporotic fractures and colorectal carcinoma.6 In the United Kingdom, this led to media headlines: “HRT does more harm than good” (Daily Mail, September 20, 2002). In August 2003, publication of the results of the MWS added further support to the view that the long-term use of HT is associated with an increase in the risk of incident and fatal breast cancer.7 The UK-based Women’s International Study on Long Duration Oestrogen
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After Menopause (WISDOM), which was similar in design to the US-based WHI, closed in October 2002 after a review of the data from the WHI by the Medical Research Council. In December 2003, the Hormonal Replacement Therapy After Breast Cancer (HABITS) trial addressing the issue of whether HT use was safe in women who had a history of breast cancer was prematurely stopped because of the increased risk of the recurrence of breast cancer in menopausal women on HT. Soon after, the UK Committee on Safety of Medicines issued guidance that HT use be restricted to the treatment of symptoms and that the smallest dose be used for the shortest duration. Finally in February 2004, the estrogen-only arm of the WHI was stopped because it showed no effect on cardiovascular disease, increased risk of stroke, and a lower risk of breast cancer that was not statistically significant. Interpretation of these studies has been highly controversial, and there is uncertainty about the implications of these findings for women using HT.

This analysis was undertaken to document trends in HT use in postmenopausal women in the United Kingdom between 2001 and 2005 by examining HT use at recruitment in a large clinical trial, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).

METHODS

UKCTOCS is a randomized controlled trial of ovarian cancer screening in the general population aimed at assessing the impact of early detection on disease mortality.

More than 1 million women aged 50 to 74 were invited from the age/sex registers of 27 participating primary care trusts in England, Wales and Northern Ireland. Women had to be postmenopausal at recruitment to be eligible for the trial. Postmenopausal was defined as more than 12 months of amenorrhea after a natural or surgical menopause or more than 12 months of HT commenced for menopausal symptoms. Exclusion criteria were bilateral oophorectomy, previous ovarian malignancy, an active nonovarian malignancy (excluding nonmelanoma skin cancer), and increased risk of familial ovarian cancer due to a family history.

Those who accepted the invitation attended a recruitment appointment and completed a baseline questionnaire. This included a question on whether they were currently using HT and, if yes, the duration of HT use. In addition, data were collected regarding hysterectomy and personal and family history of breast and ovarian cancer. Women who fulfilled eligibility criteria were randomized by a customized data management system commissioned for the trial. The trial has ethical approval from the Multicenter Regional Ethics Committee (MREC 00/08/34) and local ethics committees, and all participants signed a consent form.

Women were recruited into UKCTOCS between April 2001 and September 2005. The change in HT use over time was assessed by considering the proportion (%) of women randomized each month who were using HT when they attended for recruitment; 95% confidence intervals (CIs) for the proportion estimate were used to validate any apparent trends. Any differences in age distribution of the recruited population over time would distort the overall rate of HT use. To adjust for this, the proportion of each age group (50-54, 55-59, 60-64, and 65 or older) using HT per month was multiplied by the overall proportion of participants in each age group and added over age group. This weighting method ensured that each age group had a constant (and appropriate) influence on overall HT use. Approximate CIs for the percentage of HT use per month were calculated using the normal approximation to the binomial distribution. The adjusted estimate for proportion p and n = total recruited per month were used to estimate the respective mean and standard deviation (SD). The extent of missing data was known to be very limited, so such records were discarded in the analysis without concern for bias. The HT trends were assessed with reference to the timing of the publication of the WHI interim results (July 2002), the MWS (August 2003), and advice on safety of HT use issued by the Committee on Safety of Medicines (December 2003).

Trends and differences in HT use were also explored between women stratified according to age (50-54, 55-59, 60-64, and 65 and over) and a personal history of breast cancer. To formalize the relationship that may exist between the probability of HT use and the month of randomization as well as membership of a particular subgroup, a binary logistic regression model was fitted to the whole data set to quantify the nature of the variables’ dependencies.

RESULTS

Trial recruitment started in April 2001 and was completed in September 2005. During this period, 202,638 women were recruited and randomized. The median number of women recruited and randomized per month was 3,955 (mean 3,744.1). Randomization numbers were less than 1,000 only in the first 4 months of the trial.

All 202,638 women were 50 years of age or older, postmenopausal, with no history of ovarian malignancy or bilateral oophorectomy, and no familial risk of ovarian cancer. There was no change over time in the proportion of recruited women with a personal history of breast cancer, the number of relatives with breast or ovarian cancer, or hysterectomy. From April 2004, there was an increase in the number of women age 65 or older who joined the trial. An adjustment for age was therefore made, because older women would be less likely to take HT. There were incomplete data for 453 women, and they were excluded from the remainder of the study.

The actual percentages of women using HT at recruitment are shown in Table 1. Between April 2001 and June 2002, the average proportion of women using HT was 28% with a slight initial upward trend. This was followed by a clear downward trend in HT use starting in July 2002, coinciding with the publication of the WHI interim results. From February to September 2005, the proportion of women using HT was between 10% and 11% (averaged 10.9%). The
downward trend was confirmed in the age-adjusted proportion (with 95% CIs) of women randomized per month using HT at recruitment for the entire study period (Fig. 1). The $P$ value for the $\chi^2$ test for independence between HT use and month recruited was highly significant ($P = 0.0001$). When binary logistic regression of the probability of HT use in one month (considered as continuous and not categorical) was analyzed, the passing of a month reduced the odds of a newly randomized woman taking HT by 3% (Table 2).

There was a reduction in HT use with increasing age (Fig. 2). The overall proportion using HT was 28.9% in 50- to 54-year-old women, 24.4% in 55- to 59-year-old women, 16.6% in 60- to 64-year-old women, and 8.7% in women 65 and older (Table 1). Compared to women aged 50 to 54, the odds of using HT at recruitment was 19.0% lower in women aged 55 to 59; 46% lower in those aged 60 to 64, and 74% lower in those 65 and older, given no change in the other variables (Table 2). For all age groups, there was a decline in HT use

### Table 1. Percentage of women using hormone therapy by month and subgroup

| Quarter | No. of women | Overall (n = 202,185) | % using hormone therapy | % with personal history of breast cancer |
|---------|--------------|-----------------------|-------------------------|-----------------------------------------|
|         |              |                       | 50-54 y (n = 39,389)    | 55-59 y (n = 55,497) | 60-64 y (n = 46,989) | 65+ y (n = 60,310) | Yes (n = 7,635) | No (n = 194,550) |
| 2 Q 2001 | 620          | 26.0                  | 44.2                    | 37.8                    | 23.3                    | 5.8                    | 4.5                    | 26.8                    |
| 3 Q 2001 | 3,266        | 26.9                  | 42.8                    | 35.0                    | 22.2                    | 11.1                    | 4.0                    | 27.6                    |
| 4 Q 2001 | 8,350        | 30.0                  | 39.2                    | 37.7                    | 25.1                    | 13.9                    | 5.1                    | 30.2                    |
| 1 Q 2002 | 11,164       | 30.7                  | 42.0                    | 35.5                    | 27.9                    | 14.3                    | 3.6                    | 31.7                    |
| 2 Q 2002 | 13,138       | 26.6                  | 37.4                    | 33.2                    | 24.1                    | 12.5                    | 5.3                    | 27.3                    |
| 3 Q 2002 | 14,036       | 24.2                  | 34.9                    | 29.6                    | 22.2                    | 11.0                    | 4.2                    | 24.9                    |
| 1 Q 2003 | 15,096       | 23.4                  | 33.5                    | 28.2                    | 19.6                    | 11.0                    | 3.4                    | 24.1                    |
| 2 Q 2003 | 14,789       | 22.2                  | 30.7                    | 27.1                    | 19.6                    | 11.0                    | 3.8                    | 22.9                    |
| 3 Q 2003 | 14,215       | 21.0                  | 29.5                    | 25.6                    | 18.9                    | 10.2                    | 2.3                    | 21.7                    |
| 4 Q 2003 | 13,580       | 18.0                  | 25.2                    | 21.8                    | 15.9                    | 9.4                     | 3.5                    | 18.5                    |
| 1 Q 2004 | 15,102       | 14.4                  | 20.2                    | 18.2                    | 12.5                    | 7.0                     | 2.4                    | 14.9                    |
| 2 Q 2004 | 11,757       | 12.1                  | 18.5                    | 15.7                    | 11.8                    | 6.0                     | 1.5                    | 12.5                    |
| 3 Q 2004 | 11,702       | 10.5                  | 17.7                    | 15.8                    | 11.6                    | 5.8                     | 2.0                    | 10.9                    |
| 4 Q 2004 | 10,282       | 10.2                  | 18.9                    | 15.0                    | 12.6                    | 5.8                     | 1.8                    | 10.6                    |
| 1 Q 2005 | 12,695       | 10.9                  | 17.5                    | 13.7                    | 10.5                    | 6.7                     | 1.9                    | 11.3                    |
| 2 Q 2005 | 13,536       | 9.4                   | 17.1                    | 12.1                    | 8.9                     | 5.8                     | 2.0                    | 9.7                     |
| 3 Q 2005 | 12,087       | 11.0                  | 16.3                    | 13.3                    | 9.0                     | 7.0                     | 1.0                    | 11.4                    |
| Overall 202,185 | 18.8   | 28.9                    | 24.4                    | 16.6                    | 8.7                     | 2.9                     | 19.4                    |

$\chi^2$ test: independence of subgroup and month

* $P < 0.001$
from July 2002, although this decline was less pronounced for women aged 65 and older.

Among women with a history of breast cancer (n = 7,635), overall HT use at recruitment was 2.9% (95% CI: 2.5%-3.3%) and significantly lower compared to women with no history of the disease (19.4%) (Table 1). Having had breast cancer reduced the odds of a woman using HT by 86% compared to a woman who had not had breast cancer (Table 2). The percentage of randomized women per month taking HT in the subgroup with a history of breast cancer exceeded 10% only once, in January 2002. It was at a lower level across all time points, and there was a less discernible downward trend.

When the trends were examined separately for each trial center, the downward trends persisted.

DISCUSSION

This report highlights the steady decline in HT use in postmenopausal women in the United Kingdom in recent years. The proportion of women aged 50 to 74 using HT at recruitment to UKCTOCS, the ovarian cancer screening trial, was 29% between April 2001 and June 2002. However, from July 2002, there was a steady decline in women using HT, and by February 2005 to September 2005, only 10% to 11% of newly recruited women were using HT.

Women aged 50 to 74 were randomly invited from 27 primary care trusts in England, Wales and Northern Ireland between 2001 and 2005 to participate in a 6-year randomized controlled trial of ovarian cancer screening. This is in contrast to the more usual method of advertising the trial and allowing women to self-refer. One fifth of the total population accepted the invitation and were then sent appointments to attend for trial recruitment (manuscript in preparation). However, it is important to note that for 2001, the overall rate of HT use (35%) at recruitment in postmenopausal women aged 50 to 64 in our study was similar to the overall rate of HT use at recruitment of 33% in the MWS, which recruited between 1996 and 2001.13 Women who volunteer to participate in research are usually more educated and informed.14-16 Our cohort consists of postmenopausal women in the United Kingdom who were willing and eligible to participate in a randomized controlled trial of ovarian cancer screening. Absolute rates of HT use may therefore not apply to the entire UK female population,13 but it is the relative differences between time points that is of particular interest. Given the large size of this national cohort and the pronounced decline in HT use in recruited women, the trend observed is probably representative of a general trend in the United Kingdom. The cohort itself is fairly homogeneous as there was no change over time in the proportion of recruited women with a personal history of breast cancer, the number of relatives with breast or ovarian cancer, or hysterectomy. There was some variation in the proportion of women in various age groups

### Table 2. Results of the binary logistic regression

| Variable | Group | P   | Odds ratio | 95% CI for odds ratio |
|----------|-------|-----|------------|----------------------|
| Month    |       |     |            | Lower    | Upper    |
| Breast   | Yes   | <0.001 | 0.97   | 0.97     | 0.97     |
| Age group| 50-54 | 1.00 | 0.14       | 0.12     | 0.16     |
|          | 55-59 | <0.001 | 0.81   | 0.79     | 0.84     |
|          | 60-64 | <0.001 | 0.54   | 0.52     | 0.55     |
|          | 65+   | <0.001 | 0.26   | 0.25     | 0.27     |
| Constant |       | 0.065 | 0.97   |          |          |

![FIG. 2. Proportion of women randomized per month in each age group using hormone therapy (HT).](image-url)
over time, and because this could affect HT use, the rate of HT use was adjusted for age. The age-adjusted plots (Fig. 1) confirmed the downward trend. When the age groups were examined separately, the decline in HT use from July 2002 was present in all age groups.

Similar downward trends have been reported from the United States1,17-19 and Europe20-22 in the period 2002 to 2003 immediately after publication of the trial results. Studies reported a decline in HT prescribing in the United States from 14.6% in September 1999 to 7.9% in June 2002 in women aged 40 to 80 years,1 in The Netherlands from 10.7% in 2000 to 8.7% in 2003 in women aged 45 to 69 years,20 and in Hong Kong from 12.2% in the second half of 2000 to 4.5% by the first half of 2003 in women aged 50 or older.23 In an observational cohort study of postmenopausal US women aged 50 to 74 undergoing mammography, an 18% decline in HT use per quarter was documented during July 2002 and May 2003.18 Our report looks at the continuing trend beyond 2003. The data show a lower rate of decline (3.2% per month) in the United Kingdom, but one that continued to fall until February 2005, when it stabilized. An annual report on prescription costs for England by the Department of Health support these findings. In 2001, there were 6.3 million HT prescriptions dispensed in England, and by 2004, this had fallen to 3.8 million.24

The timelines suggest that the decline is related to the publication of the WHI and MWS results. In the United States, the dissemination of the WHI HT trial results had an immediate impact on the discontinuation of HT.17 Our data suggest that in the United Kingdom, the publication of the US study was followed by a gradual decline in HT use, which fell more steeply after publication of the British MWS in August 2003. The difference in impact of the two trials on HT use was also noted in The Netherlands with a modest decline in HT prescribing after the publication of the WHI study, followed by a dramatic decrease in the prescribing of HT after release of results from the MWS.20

Reports from small longitudinal cohort studies support the decline in HT use to be related to the WHI trial.25,26 The decline was less pronounced in Germany, where, in a survey of 8,380 women (mean age 56.1 years), only 25.7% reported stopping HT in response to the WHI results,27 as opposed to 40% and 60% in New Zealand26 and the United States,25 respectively. In a recent study from the United Kingdom, the overall percentage of HT users in a cohort of 1,387 women aged 57 years decreased from 31% in January 2002 to less than 26% by February 2003.28

A number of factors may have contributed to this decline. Media coverage of the WHI study had a significant influence on women’s use of HT.29 There was a misunderstanding about the magnitude of risks and benefits. The original publication and most of the ensuing publicity from WHI phrased the risks as a percentage of increase (or decrease) of the relative risk. For example, there was a 24% increased relative risk of breast cancer per year in the HT group. The general public, not understanding the concept of relative risk, interpreted this statement as a 24% chance of developing breast cancer each year on HT.30 An evaluation study of educational intervention on the HT continuation rate in Slovenia confirmed that the main reason for discontinuing HT was fear of breast cancer, intensified by the media.31

A recent Cochrane review identified five studies that evaluated healthcare utilization before and after media coverage of specific events.32 Each found changes in use: favorable publicity was associated with higher use and unfavorable publicity with lower use. The Cochrane review concluded that media reports played an important role in influencing the public’s use of healthcare interventions. Media coverage as distinct from the scientific importance of the work also plays an important role in transmitting knowledge to the scientific community.33 In addition, guidance circulated by most healthcare providers about the implications for prescribing HT probably contributed to the observed changes.24 as did the advice given by physicians as women who continued taking HT did so largely based on their physician’s advice.35 Interrelated with all this, reduced promotion of HT by the pharmaceutical companies may have further played a role in the decrease in prescriptions.36

Since publication of the WHI and MWS findings, use of complementary therapies seems to be on the increase,37,38 although no alternative therapy has been cited in the literature or reported by the women surveyed to be as successful as estrogen for symptom relief.39,40 Future patterns of HT use remain uncertain but will likely be shaped by multiple influences, including professional and public attitudes toward risks and benefits and pharmaceutical marketing. The data about the pros and cons of HT use remain confusing, but this report indicates that there probably has been a steady decrease in HT use among postmenopausal women in the United Kingdom, similar to trends in the United States and Europe.

CONCLUSIONS
The steady decline in HT use in postmenopausal women recruited into UKCTOCS is likely to reflect general trends in the UK population and is probably related to the premature closure of the large HT trials and the ensuing publicity.

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