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Decline in use of hormone therapy amongst postmenopausal women in the UK

Running title: Decline in HT use in the UK

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Structured Abstract

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

Design Between April 2001 and September 2005, 202,638 postmenopausal women aged 50-74 and with no history of bilateral oophorectomy, were recruited to the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The proportion of women randomised each month who were using HT was calculated. The trend in HT use was assessed with reference to the publication of the WHI interim results (July 2002), the MWS (August 2003) and advice from the UK Committee on Safety of Medicines (Dec 2003).

Results The median number of women recruited and randomised per month was 3,955 (mean 3,744). The proportion of randomised 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 10-11% of newly recruited women were using HT. This trend was present in all age groups. However in current users, average duration of HT use remained steady at 10-11 years.

Conclusions There was a steady decline in HT use in postmenopausal women at recruitment into UKCTOCS between April 2001 and Sept 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.

Keywords: hormone/hormone replacement therapy; change in use; United Kingdom; UKCTOCS

Introduction

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 50-64 years used HT.¹ Following observational studies showing significant benefits in 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 1995.¹

In the late 1990s, large randomised controlled trials in the US (Women's Health Initiative, WHI) and observational studies in the UK (Million Women Study, MWS) were instituted to confirm the findings of the smaller studies. The estrogen and progestogen 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 felt to outweigh any benefits from reduced risks of osteoporotic fractures and colorectal carcinoma.⁶ In the UK, this led to media headlines - "HRT does more harm than good" (Daily Mail, 20th September 2002). In August 2003, publication of results from 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 WISDOM trial (Women's International Study on long Duration Oestrogen after Menopause) which was similar in design to the US-based WHI, closed in October 2002 following review of data from the WHI by the Medical Research Council.⁸ In December 2003, the HABITS trial addressing the issue of whether HT use was safe in women who had a previous history of breast cancer was prematurely stopped because of the increased risk of recurrence of breast cancer in menopausal women on HT.⁹ Soon after, the UK Committee on Safety of Medicines (CSM) issued guidance that HT use be restricted to treatment of symptoms and that the smallest dose be used for shortest duration. Finally in February 2004, the estrogen only arm of the WHI initiative was stopped as it showed no effect on cardiovascular disease, increased risk of stroke and a lower risk of breast cancer that was not statistically significant.^{10,11} Interpretation of these studies have been highly controversial and there is uncertainty about the implications of these findings for women using HT.¹²

This analysis was undertaken to document trends in HT use in postmenopausal women in the UK between 2001 to 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 randomised controlled trial of ovarian cancer screening in the general population aimed at assessing the impact of early detection on disease mortality.

Over 1 million women aged 50-74 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 >12 months amenorrhoea following a natural or surgical menopause or >12 months of HT commenced for menopausal symptoms. Exclusion criteria were

bilateral oophorectomy, previous ovarian malignancy, an active non-ovarian malignancy (excluding non melanoma 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 was collected regarding hysterectomy and personal and family history of breast and ovarian cancer. Women who fulfilled eligibility criteria were randomised by a customised data management system commissioned for the trial. The trial has ethical approval from the multicentre 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 randomised each month who were using HT when they attended for recruitment. 95% confidence intervals 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 HRT use. To adjust for this, the proportion of each age group (50-54, 55-59, 60-64 and 65 or over) 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 confidence intervals for the percentage 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. The extent of missing data was known to be very limited and so such records were discarded in the analysis without concern of 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 CSM (Dec 2003).

Trends and differences in HT use were also explored between women stratified according to age (50-54, 55-59, 60-64 and 65 or over) and a personal history of breast cancer. To formalise the relationship that may exist between the probability of HT use and the month of randomisation as well as membership of a particular subgroup, a binary logistic regression model was fitted to the whole dataset 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 randomised. The median number of women recruited and randomised per month was 3,955 (mean 3,744.1). Randomisation numbers were <1,000 only in the first four months of the trial.

All 202,638 women were ≥ 50 years of age, postmenopausal, with no history of ovarian malignancy or bilateral oophorectomy, or familial risk of ovarian cancer. There was no change over time in the proportion of recruited women with a personal history of breast cancer, number of relatives with breast or ovarian cancer or

hysterectomy. From April 2004 there was an increase in the number of women aged over 65 who joined the trial. An adjustment for age was therefore made, as older women would be less likely to take HT. 453 women had incomplete data and 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 10-11% (averaged 10.9%). The downward trend was confirmed in the age-adjusted proportion (with 95% confidence intervals) of women randomised per month using HT at recruitment for the entire study period (Figure 1). The p-value for the χ^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 on month (considered as continuous and not categorical) was analysed, the passing of a month reduced the odds of a newly randomised woman taking HT by 3% (Table 2).

There was reduction in HT use with increasing age (Figure 2). The overall proportion using HT was 28.9% in 50-54 year women, 24.4% in 55-59, 16.6% in 60-64 and 8.7% in over 65 (Table 1). Compared to women aged 50-54, the odds of using HT at recruitment was 19.0% lower in women aged 55-59; 46% lower in those aged 60-64 and 74% lower in those aged over 65, given no change in the other variables (Table 2). For all age groups, there was a decline in HT use from July 2002, although this decline was less pronounced for women over the age of 65.

Among women with a past history of breast cancer ($n=7635$), 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 woman who has not had breast cancer (Table 2). The percentage of randomised women per month taking HT in the subgroup with a past 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 discernable downward trend.

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

Discussion

This report highlights the steady decline in HT use in postmenopausal women in UK in recent years. The proportion of women aged 50-74 using HT at recruitment to the ovarian cancer screening trial, UKCTOCS, 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 10-11% of newly recruited women were using HT.

Women aged 50-74 were randomly invited from 27 primary care trusts in England, Wales and Northern Ireland between 2001 and 2005 to participate in a 6 year randomised control 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 (paper in preparation). However it is important to note that for 2001, the overall rate of HT use (35%) at recruitment in postmenopausal women aged 50-64 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 UK who were willing and eligible to participate in a randomised control 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 UK. The cohort itself is fairly homogenous as there was no change over time in the proportion of recruited women with a personal history of breast cancer, number of relatives with breast or ovarian cancer or hysterectomy. There was some variation in the proportion of women in various age groups over time and as this could impact on HT use, the rate of HT use was adjusted for age. The age-adjusted plots (Figure 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 USA¹⁷⁻¹⁹ and Europe²⁰⁻²² in the period 2002-2003 immediately following publication of the trial results. Studies reported a decline in HT prescribing in the USA from 14.6% in September 1999 to 7.9% in June 2002 in women aged 40-80 years;¹⁹ The Netherlands from 10.7% in 2000 to 8.7% in 2003 in women aged 45-69 years²⁰ 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 above.²³ In an observational cohort study of postmenopausal US women aged 50-74 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 shows a smaller rate of decline (3.2 % per month) in the UK, 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 USA, the dissemination of the WHI HT trial results had an immediate impact on the discontinuation of HT.¹⁷ Our data suggests that in the UK, 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 fall 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, however 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 results²⁷ as opposed to 40% and 60% in the

reports from New Zealand²⁶ and USA²⁵ respectively. In a recent paper from the UK the overall percentage of HRT users in a cohort of 1387 women aged 57 years declined 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 percent 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 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 health care utilization before and after media coverage of specific events.³² Each found changes in utilization: favourable publicity was associated with higher use, unfavourable publicity with lower use. The Cochrane review concluded that media reports played an important role in influencing the public's use of health care 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 health care providers about the implications for prescribing HT probably contributed to the observed changes³⁴ as did the advice given by physicians as women who continued to taking HT did so largely based on their physician's advice.³⁵ Interrelated with all of this, reduced promotion of HT by the pharmaceutical companies may have further played a role in the decline in prescriptions.³⁶

Since 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 oestrogen for symptom relief.^{39,40} Future patterns of hormone therapy 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 decline in HT use amongst postmenopausal women in the UK, similar to trends in the USA and Europe.

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TABLE 1: PERCENTAGE OF WOMEN USING HRT BY MONTH AND BY SUB-GROUP

| | No of women | Overall | Age Group (years) | | | | Personal history of breast cancer | |
|----------------|-----------------|--|-------------------|-------------|-------------|------------|-----------------------------------|-------------|
| | | | 50 - 54 | 55 -59 | 60 -64 | 65+ | Yes | No |
| | 202,185* | | 39389 | 55497 | 46989 | 60310 | 7635 | 194550 |
| Quarter | | % using HT | | | | | | |
| 2 Q 2001 | 620 | 26.0 | 44.2 | 37.8 | 23.3 | 5.8 | 4.5 | 26.8 |
| 3 Q 2001 | 3266 | 26.9 | 42.8 | 35.0 | 22.2 | 11.1 | 4.0 | 27.6 |
| 4 Q 2001 | 6770 | 30.0 | 42.9 | 36.5 | 27.2 | 11.7 | 6.5 | 30.8 |
| 1 Q 2002 | 8350 | 29.5 | 39.2 | 37.7 | 25.1 | 13.9 | 5.1 | 30.2 |
| 2 Q 2002 | 11164 | 30.7 | 42.0 | 35.5 | 27.9 | 14.3 | 3.6 | 31.7 |
| 3 Q 2002 | 13138 | 26.6 | 37.4 | 33.2 | 24.1 | 12.5 | 5.3 | 27.3 |
| 4 Q 2002 | 14036 | 24.2 | 34.9 | 29.6 | 22.2 | 11.0 | 4.2 | 24.9 |
| 1 Q 2003 | 15096 | 23.4 | 33.5 | 28.2 | 19.6 | 11.0 | 3.4 | 24.1 |
| 2 Q 2003 | 14789 | 22.2 | 30.7 | 27.1 | 19.6 | 11.0 | 3.8 | 22.9 |
| 3 Q 2003 | 14215 | 21.0 | 29.5 | 25.6 | 18.9 | 10.2 | 2.3 | 21.7 |
| 4 Q 2003 | 13580 | 18.0 | 25.2 | 21.8 | 15.9 | 9.4 | 3.5 | 18.5 |
| 1 Q 2004 | 15102 | 14.4 | 20.2 | 18.2 | 12.5 | 7.0 | 2.4 | 14.9 |
| 2 Q 2004 | 11757 | 12.1 | 18.5 | 15.7 | 11.8 | 6.0 | 1.5 | 12.5 |
| 3 Q 2004 | 11702 | 10.5 | 17.7 | 15.8 | 11.6 | 5.8 | 2.0 | 10.9 |
| 4 Q 2004 | 10282 | 10.2 | 18.9 | 15.0 | 12.6 | 5.8 | 1.8 | 10.6 |
| 1 Q 2005 | 12695 | 10.9 | 17.5 | 13.7 | 10.5 | 6.7 | 1.9 | 11.3 |
| 2 Q 2005 | 13536 | 9.4 | 17.1 | 12.1 | 8.9 | 5.8 | 2.0 | 9.7 |
| 3 Q 2005 | 12087 | 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 |
| | | <i>χ^2 test: independence of (sub-)group and month</i> | | | | | | |
| p-value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 |

* Incomplete data in 453 women.

TABLE 2: RESULTS OF THE BINARY LOGISTIC REGRESSION

| Variable | Group | p-value | OR | 95% CI for OR | |
|-----------|-------|---------|------|---------------|-------|
| | | | | Lower | Upper |
| Month | | <0.001 | 0.97 | 0.97 | 0.97 |
| Breast | Yes | <0.001 | 0.14 | 0.12 | 0.16 |
| Age Group | 50-54 | | 1.00 | | |
| | 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 | | .065 | 0.97 | | |

Figure legends

Figure 1. Percentage of women randomised each month who were using HRT

Figure 2. Proportion of women randomised per month in each age group using HRT



