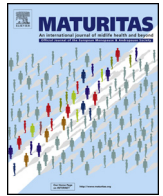




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Menopausal hormone therapy use in 17 European countries during the last decade

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ABSTRACT

Introduction: The first ‘Women’s Health Initiative’ (WHI) randomised controlled trial assessed use of continuous combined menopausal hormone therapy (cc-MHT). It was prematurely stopped because of an increased invasive breast cancer (BC), coronary heart disease (CHD), stroke and pulmonary embolism risk. Consequently, scientific societies recommended use of MHT at the lowest effective dose for the shortest duration. As a result, a sharp decline in MHT use occurred worldwide.

Aim: To report in a uniform way the change in MHT use in European countries. To evaluate whether the variability of the MHT changes were related to some medical indicators.

Materials and methods: IMS Health provided MHT sales data for the years 2002 till 2010 for 17 countries. We tested several hypotheses to explain the heterogeneity of MHT use changes.

Results and discussion: In 2002, the estimated MHT rate in women 45–69 years old varied considerably between countries ranging from less than 5% to more than 25%. In all countries a profound decrease occurred between 2002 and 2010, ranging from 50% to 77%. By the end of 2010, the MHT uptake was lower than 10% in all countries except in Finland. MHT use change was not correlated to MHT use and prevailing BC incidence at baseline, nor to the number of gynaecologists per 100,000 women or to the level of information about MHT.

Conclusion: The global MHT use experienced a sharp decrease in all the analysed countries, although some variability exists. The decrease was unrelated to the assessed parameters.

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1. Introduction

Ten years ago, the gynaecological community was perplexed when the ‘Women’s Health Initiative’ (WHI) decided to stop prematurely one of its clinical trials on menopausal hormone therapy (MHT) in the United States [1]. This randomised controlled trial evaluated whether the association of a continuous use of conjugated estrogens (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) versus a placebo would reduce the risk of a number of diseases, in a large population of moderately elderly postmenopausal women [1]. In this study, this MHT regimen increased the risk of

invasive breast cancer (BC), coronary heart disease (CHD), stroke and pulmonary embolism more often than it reduced the risk of osteoporosis and colorectal cancer. MHT users had a BC relative risk of 1.26 (95%CI 1.00–1.59) compared with non-users. Successive publications from the WHI group between 2003 and 2012 moderated these findings [2–5]. Moreover, in younger patients (aged 50–60), the use of oestrogen only therapy may reduce the CHD risk; while on the contrary, an increased CHD risk was seen in elderly women [4]. On the other hand, further studies showed that the use of CEE 0.625 mg as an only therapy in hysterectomized women was not associated with an increased BC risk [2]. More recently, a reduced risk of BC incidence (0.27% versus 0.35% per year ($P=0.02$)) and mortality (0.009% versus 0.024% per year ($P=0.03$)) were even reported in this cohort of estrogens only users [2]. In Europe, the Million Women Study (MWS), a prospective cohort study, showed an increase of BC risk for all MHT regimens in current users (RR 1.43 (95%CI 1.36–1.50)). The magnitude of this risk varied according to the MHT regimen used [6]. It is likely that this study amplified

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the negative impression of MHT both in the lay press and the general public, resulting in further decrease of MHT use. Later results showed that BC risk was greater if MHT started at around the time of menopause than later [7].

Following the first WHI and MWS results, women were frightened by initial results and the possible risk of developing BC using MHT. Regulatory Agencies and scientific societies recommended use of MHT at the lowest effective dose for the shortest possible duration. As a result, a sharp decline in MHT use occurred worldwide [8].

Even if, in some countries, a BC incidence decrease was observed before the publication of the WHI trial (following the publication of the HERS study according to some authors [9,10]), publications from United States showed a sharp decline in MHT use after 2002 [11–14]. This decrease on MHT use was also described in many European countries [8]. Before the first WHI publication, the European MHT market was characterised by a large variation in MHT formulations and by a large heterogeneity of MHT use [15]. The aim of our study was to report in a uniform way the change in MHT use for different formulations, during the last decade, in 17 European countries and to evaluate whether changes in MHT use were related to some medical indicators such as initial MHT level or information on MHT, as well as BC incidence.

2. Materials and methods

2.1. MHT data extraction

Sales data of all available MHT were provided by IMS Health (www.imshealth.com), per country, for the years 2002 till 2010 (sales data were not available before 2002). The world company IMS Health connects healthcare data on diseases, treatments, costs and outcomes. Data were available for seventeen European countries only. The MHT sales data were presented in terms of standard “dose” units sold: the number of counting units sold divided by the standard unit factor which is the smallest common dose of a product form as defined by IMS Health [16].

For each of the 17 countries, we used the following proxy to estimate the proportion of women 45–69 years old using MHT: the ratio $(\# \text{ standard 'dose' units} \times 0.90) / (\# \text{ women } 45\text{--}69 \times 365)$. The correction factor 0.90 in the numerator was applied to correct for the fact that not all MHT users were 45–69 years old, based on preliminary analysis [16]. The factor 365 was used in the denominator because sold standard dose units were provided per year.

Sales data were provided for the Anatomical Therapeutic Chemical (ATC) classes G03C (estrogens), G03F (progestogens and estrogens in combination), G03CX01 (tibolone) and G02F (topical sex hormones). The last class was not included in the estimation of total MHT use. We had no way to know if estrogens, in the ATC class G03C, were sold alone or combined to a separated progestin, but we hypothesise that the same proportion of women use unopposed oestrogen or combined with a separated progestin in between countries and within each country during the studied period.

2.2. Hypotheses explaining changes of MHT use

We further tested the following hypotheses to explain the heterogeneity of MHT changes of use in Europe during the last decade: the decrease in MHT use was associated (a) with the initial level of MHT use in each country (b) with the prevailing BC incidence in each country; (c) with the number of practicing gynaecologists per 100,000 women; and (d) was associated with the perceived level of information on MHT. The years we tested varied according to availability of each of these data.

BC incidence data were obtained from the National Cancer Registries of the respective countries for the year 2000. Of the seventeen countries with available MHT data, nine had BC incidence data available in the year 2000: Austria, Denmark, Finland, Ireland, Norway, the Netherlands, Sweden, Switzerland and United Kingdom (UK) (by combining the data from England, Wales, Scotland and Northern Ireland).

Data on perceived level of information on MHT were extracted from the Eurobarometer 2007 report “Health in the European Union” for the year 2006 (http://ec.europa.eu/health/ph_publication/eb_health_en.pdf) [17].

The number of gynaecologists per 100,000 women was extracted from the European report OECD indicators – Health at a glance 2011, page 69 (available for the years 2000 and 2009) [18].

2.3. Statistical analyses

Associations were assessed using a weighted Pearson’s correlation coefficient. We used the number of women per country in the age class 45–69 years as weight in order to adjust for the difference in population size between different countries [16]. We considered a *P*-value <0.05 as significant. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all analyses.

3. Results

3.1. Global MHT use

In 2002, the estimated MHT rate in women 45–69 years old varied considerably between countries, ranging from less than 5% in some countries such as Spain, Italy and Greece to more than 25% in Sweden (Figs. 1 and 2A). Globally, Northern European countries had rather high MHT uptake while Southern European countries had low uptakes (Figs. 1 and 2A). In all countries a profound relative decrease occurred between 2002 and 2010, ranging from 50% to 77%. In 2010, the MHT uptake was lower than 10% in all countries with the exception of Finland (Figs. 1 and 2B). The sharpest relative decreases were observed in Austria (77%) and Sweden (76%) and the lowest in Finland (50%) and Switzerland (54%).

3.2. MHT regimens

3.2.1. Estrogens only or combined to a separate progestin

The change of the use of estrogens only or combined to a separate progestin is presented in Fig. 3A. In 2002, the rate varied in women 45–69 years old from <1% in Greece to 11.5% in Finland. Globally estrogens only or combined to a separate progestin decreased by at least 50% in all countries, with exception of Switzerland (45%), between 2002 and 2010. In 2010, the rate of estrogens only or combined to a separate progestin use was 5.4% in Finland, 3.8% in Switzerland, and less than 3% in all the other countries.

3.2.2. Combined regimens of estrogens and progestins

Fig. 3B shows the change of the use of estrogens combined to progestins for women aged 45–69 years old, which ranged from 1.4% (Italy) to 15.0% (Sweden) in 2002 and lowered to a range of 0.6% (Italy and Spain) to 5.8% (Finland) in 2010. All countries had a decrease of at least 50% between 2002 and 2010. Five countries had a decrease of at least 80%: Austria, France, Ireland, the Netherlands and Sweden.

Overall, Northern countries had a higher use of estrogens only and estrogens combined to progestins compared to Southern countries in the year 2002 and this was still the case in 2010

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