Maturitas 84 (2016) 81–88

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Menopausal hormone therapy use in relation to breast cancer incidence in 11 European countries

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form
17 November 2015
Accepted 18 November 2015

Keywords:
Menopause hormone therapy
Breast cancer
Incidence
Sales
Europe

ABSTRACT

Introduction: The use of menopausal hormone therapy (MHT) has decreased in many countries in the past 10 years. This is a consequence of the initial publication of the results of the Women's Health Initiative (WHI) randomized trial of estrogen plus progestin. In various countries, further studies then analyzed the incidence of breast cancer (BC) in relation to changes in MHT use. Some reported a decreased BC incidence following cessation of MHT, but others did not. This may reflect differences in BC incidence, in MHT use or in confounding factors, but also in study methodology.
Aim: To analyze the changes in BC incidence and MHT use, using the same methodology, in 11 European countries.
Materials & method: We limited the study to women between the ages of 45 and 69. BC incidence data were provided from cancer registries. MHT sales data were extracted from health sales databases for the years 2003–2013. The association between BC incidence and the rate of MHT use during the past year in Europe was assessed using linear mixed models.
Results: A drop in MHT sales was consistent in all countries for the whole period of follow-up. This was not the case for BC incidence. We found no evidence of a relation between BC incidence and MHT sales in the past year, except for sales of tibolone.
Conclusions: The longer observation period did not confirm the results of studies that had a shorter follow-up, except in relation to tibolone. The role of confounding factors needs to be clarified.
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1. Introduction

The first publication of results from the randomized controlled trial (RCT) by the Women's Health Initiative (WHI) comparing women treated with conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) versus placebo concluded that an increased risk of breast cancer (BC) was associated with the use of menopausal hormone therapy (MHT) [1]. Since then, MHT consumption has decreased in most countries and several studies have reported a coincident decrease in BC incidence [2–10]. The extent of this decrease and the length of time between the drop in MHT use and the change in BC incidence have varied between countries [3,7]. This may reflect differences in BC incidence, in MHT use or in confounding factors, but also in study methodology.

The type and regimen of MHT may influence the risk of BC [1,14]. Indeed, in the publications on the WHI RCT the authors reported an increased BC incidence with combined estrogen–progestin MHT. The use of estrogen only was paradoxically associated with a decrease in BC incidence [1,11]. Several other studies have reported differences in risk related to the type of MHT regimen [12–14]. In the latest report of the E3N study, a French observational study of teachers, a smaller increase in BC risk was reported among estrogen-only users and among users of estrogen combined with micronized progesterone or dydrogesterone as compared with users of estrogens combined with MPA or norethisterone acetate (NETA) [12,13]. Similarly, a Finnish observational study reported that sequential progestin use resulted in a smaller increased risk of BC than did continuous progestin use, but one should note that in this study most patients used NETA [14].

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http://dx.doi.org/10.1016/j.maturitas.2015.11.010
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The prevalence of MHT use may also influence changes in the prevalence of BC since the impact of MHT prescription on the incidence of BC is expected to be small in countries where use is low [15].

BC incidence may also depend on confounding factors such as BC screening [16]. Screening varies widely between countries: in some countries, there is no screening at all; in others, screening has been implemented but is still being developed; in yet other countries, screening has been in place for many years [17]. The timing of the introduction of screening may have an influence on reported rates of BC, as the apparent incidence of BC will increase immediately after the implementation of screening [16]. Moreover, the drop in MHT use also seems to be associated with a drop in mammography rates [18]. This makes the analysis of the relation between MHT and BC even more complicated.

We previously conducted a systematic review of publications concerning BC incidence in relation to MHT use [15]. We observed that data on BC incidence and MHT use were taken from many sources and approximations were often needed when analyzing them. The reported period of evaluation varied considerably between studies and different models were used to assess a possible relation between BC incidence and MHT use [15].

One should therefore be cautious when drawing conclusions from these studies about a possible relation between a drop in MHT consumption and subsequent changes in BC incidence.

This study analyses changes in BC incidence in relation to MHT sales data, using the same methodology, in 11 European countries.

2. Materials and method

2.1. Population

In order to assess the possible association between MHT and BC, we restricted the study to women between the ages of 45 and 69, as most women using MHT fall into this age group, according to previous analyses [19].

2.2. Breast cancer data

We initially sought information for 40 European countries (Fig. 1). Countries with no national cancer registry were excluded from the study ($n = 15$) and we contacted 25 national cancer registries to obtain BC incidence data. Usable replies were obtained from 20 European countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Malta, the Netherlands, Norway, Poland, Slovakia, Slovenia, Sweden, Switzerland and the United Kingdom (UK) (England, Wales, Scotland and Northern Ireland). A further nine countries were excluded because of a lack of data on MHT (see below). For the 11 remaining countries, BC data were available from 2000 to 2011 for Austria, Ireland and Switzerland, from 2004 to 2012 for Belgium, from 2000 to 2012 for Denmark, Norway, the Netherlands, Sweden, the UK and Finland, and from 2003 to 2011 for Germany [20–30]. The BC incidence for the UK was calculated from the BC incidence in England, Wales, Northern Ireland and Scotland by applying a weighting factor based on the size of the population of women aged 45–69 years: 83% England, 5% Wales, 3% Northern Ireland and 9% Scotland [31].

2.3. Menopause hormone therapy data

MHT sales data were extracted from IMS Health sales databases for 17 European countries for the years 2003–2013. The MHT sales data were presented in terms of 'standard dose' units sold: the number of units sold divided by the standard unit factor, which is the smallest common dose of a product form as defined by IMS Health.

The proportion of women between the ages of 45 and 69 using MHT was estimated as follows: ((#'standard dose' units) × 0.90)/((#women) × 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 the preliminary analysis made in Belgium [19]. The factor 365 was used in the denominator because standard dose units were annual figures.

2.4. Statistical analyses

We were able to obtain both BC incidence data and MHT sales data for 11 countries: Austria, Belgium, Denmark, Finland, Germany, Ireland, Norway, the Netherlands, Sweden, Switzerland and the United Kingdom (Fig. 1).

The association between BC incidence and the rate of MHT use in the past year in Europe was assessed, using linear mixed models in order to take into account the dependency between the subsequent data points. We also repeated the analyses considering use of MHT either two or three years before the BC incidence period. We used an unstructured correlation matrix [32]. We adjusted for the number of women per country in the age group 45–69 years, in order to correct for the differences in population size between countries. As linear mixed models are not robust to outliers, we performed the analyses twice, with and without the outlying values from Denmark for the years 2008–2010 and from Germany for the years 2008 and 2009 [32]. We considered a p-value < 0.05 as significant. SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

3. Results

Fig. 2 shows the changes in BC incidence between 2000 and 2012 in women aged 45–69 years for the 11 included European countries.

The changes in BC incidence vary between the countries. The highest overall BC incidence was observed in Belgium and the lowest in Austria (360.3 and 207.4 per 100,000 women in 2004, respectively). An important BC incidence increase was observed during the years 2008–2010, in Denmark, Germany and Ireland. In Denmark the BC incidence rose by 17% in 2008 from 277.9 per 100,000 women in 2007, to 324.6 per 100,000 women, and again by 31% in 2009 (425.4 per 100,000 women). In Germany, relative to the 2007 figure (266.7 per 100,000 women), in 2008 the BC incidence had increased by 12% in 2008 (297.5 per 100,000 women) and by 11% in 2009 (296.3 per 100,000 women). In Ireland an increase of 13% was observed in 2008 as compared with 2007 (311.8 versus 276.5 per 100,000 women).

During the follow-up period, the BC incidence slightly decreased in Belgium, Norway, Sweden and Switzerland; it moderately increased in the UK, Finland and the Netherlands; and it remained stable in Austria.

Fig. 3A shows the changes in the estimated MHT use in women aged 45–69 for the 11 European countries from 2003 to 2013: MHT sales decreased in all of these countries, the drop varying between 42.1% and 76%. Finland, Sweden and Belgium had the highest use of MHT in 2003 (22.9%, 22.3% and 18.8%, respectively). This use decreased to 13.2%, 5.3% and 9.7% in the year 2013. The Netherlands had the lowest MHT use for the whole period: MHT use decreased from 4.4% in 2003 to 1.3% in 2013.

Fig. 3B–D shows, respectively, the changes from 2003 to 2013 in the estimated use of estrogens-only or estrogens prescribed with a separate progestin, of estrogens combined with a progestin and of tibolone. The sale of estrogens only or prescribed with a separate progestin decreased in all of the countries, the drop ranging from 32.9% to 74.4%; the sale of estrogens combined with a progestin also decreased in all of the countries, by 44.8% to 78.4%. Similarly,

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