Use of hormone therapy (HT) among Swedish women with contraindications - A pharmacoepidemiological cohort study

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Use of Hormone Therapy (HT) among Swedish women with contraindications – a pharmacoepidemiological cohort study.

Running title: Hormone use in women with contraindications

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Abstract:

Objectives: To assess how women with breast cancer (BC), endometrial cancer (EC), and/or pulmonary embolism (PE) were dispensed menopausal hormone therapy (HT) in Sweden.

Study design: A retrospective study on Swedish women 40 years or older at 31 December 2005 (n=2,863,643), followed through December 2011. Record-linkage of three mandatory national healthcare registries, Swedish Prescribed Drug Register, National Inpatient Register and Cancer Register. New users defined as having a first dispensation after at least 9-month run-in, and thus possible to identify from April 2006. New users with at least one of the diagnoses BC, EC or PE before the first dispensation were classified having a relative or absolute contraindication for HT.

Main outcome measures: To measure the relative risk of having HT dispensed after being diagnosed with BC, EC and/or PE.

Results: In total 171,714 had at least one of the diagnoses BC, EC and/or PE. The relative risk of having hormone therapy dispensed (current and new users) after being diagnosed with any of the diagnoses was significantly lower (PE: IRR 0.11; 95% CI 0.10-0.12 / BC: IRR 0.12; 95% CI 0.11-0.13 / EC: IRR 0.43; CI 0.40-0.46) than in women without these diagnoses.

Conclusions: One in about 250 women started treatment with HT after being diagnosed with either BC, PE or EC. *Swedish prescribers seem to be well aware of the recommendations for HT-use in women with contraindications. A few women, however, are prescribed HT despite BC, EC or PE, possibly after careful risk- and benefit evaluation and shared consent. Women with a history of PE were prescribed transdermal HT to a larger extent than women in general in line with results from observational studies.*

Key words: Menopause, Estrogen, Hormone therapy, Contraindications, Pharmacoepidemiology

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1. Introduction

Hormone therapy (HT) is an effective treatment for vasomotor symptoms (i.e hot flushes and night sweats) in peri- and postmenopausal women [1]. During the last decades treatment recommendations have been changed several times [2,3]. Results have been published from sub-analyzes from the *Heart and Estrogen/progestin Replacement Study* (HERS) [4], *Women Health Initiative* (WHI) [5, 6] and the *Million Women Study* (MWS) [7] studies, including analyses of risks associated with treatment with estrogen only (ET) and estrogen plus progestogen (EPT) [8]. Even though the initial alarming reports have been modified over time HT use has dramtacially decreased in many countries [9-11]. According to the Swedish Prescribed Drug Registry only about 6 percent of women 47-56 years old used HT in Sweden 2010-2012. In a questionnaire study only 5.5% of 47-56 years old women were using HT in 2010 in the county of Östergötland, Sweden [12].

The incidence in breast cancer (BC), endometrial cancer (EC), and venous thromboembolisms (VTE) increases with age. HT increases the risk of VTE and stroke [13-16] whereas EPT but not ET increases the risk of BC [7,17,18]. On the other hand unopposed ET increases EC when treating non-hysterectomised women [19], whereas continuous combined EPT decreases the incidence of EC [20]. A global consensus statement [3] stated that oral HT increases the risk of VTE (i.e pulmonary embolism (PE) and deep vein thrombosis (DVT)). Retrospective analyses of HT use suggest that transdermal regimens are

not as prothrombotic as oral HT, with lower VTE risk, but this has not been evaluated in randomized controlled trials (RCT) [15].

The risk of BC is probably primarily associated with the addition of progestogens in HT and EPT significantly increases the risk of BC [5,7]. The HABITS-study [21] showed an increased risk of recurrence in BC survivors who used EPT and the LIBERATE-study [22] showed a higher rate of BC recurrence in the tibolone treatment group compared with the placebo group.

Thus most treatment recommendations strongly advice against HT in women with present or previous BC [2,3] and with a history of VTE, whereas the recommendations regarding survivors of EC are less well defined.

In Sweden, there is a unique history of national public health registers providing unique data on the entire population. The personal identity number (PIN) introduced in Sweden in 1947 can be used to follow individuals longitudinally and link information from several registers [23]. The Swedish National Inpatient Register (IPR) launched in 1964 has nearly complete coverage from 1987 and currently registers 99% of all somatic hospital discharges with 85-95% valid diagnoses. The IPR diagnoses are coded according to the international classification of disease (ICD) system, adapted from the WHO [24] and derived from the ICD-10 system, created in 1997 and with yearly up-dates. There is no complete coverage, however, of the diagnoses of patients attending out-patient clinics or primary care.

The Swedish Prescribed Drug Registry established 1999 at the National Board of Health and Welfare consists of information on all prescribed drugs dispensed to the entire population at pharmacies in Sweden [25]. Since July 2005 the PIN has been included for every entry and only missing for <0.3% of all dispensations.

The Swedish Cancer Registry was founded in 1958 and covers the whole population and a study from 2008 found an estimated underreporting of 4% in comparison to the IPR [26].

Since the systems of registers in Sweden are population-based, well designed, have high validity and coverage and are controlled by the National Board of Health and Welfare they constitute a unique opportunity to study earlier events/diseases in life and relate them to current or former use of HT.

The objective of this pharmacoepidemiological study was to describe the number of HT users in Sweden previously diagnosed with BC, EC and/or PE. A secondary objective was to describe the proportion of clinical specialties among physicians who initiate and continue prescribing HT for women with a contraindication such as BC, EC and/or PE and to describe what kind of regimens the physicians prescribe to women with a history of PE.

2. Methods

2.1 Study population.

The study population consisted of all women, registered in Sweden, who were alive and at least 40 years old on 31 December 2005. These women were followed from 1 July, 2005 until 31 December, 2011.

2.2 Definitions of HT and ICD-codes.

Drugs for systemic HT for vasomotor symptoms were defined as oral and transdermal products within the Anatomic Therapeutic Chemical classification system (ATC-groups) shown in Table 1. No injectable preparation for HT is used in Sweden. Data on dispensed drugs from the Swedish Prescribed Drug Register were extracted by the National Board of Health and Welfare and linked to demographic data from Statistics Sweden. The age of the women is reported as the age at 31 December 2005.

The Swedish Prescribed Drug Register contains information on the prescribers' specialties. The specialty of the prescriber was defined as the specialty (e.g. gynecologist or gynecological oncologist) in at least one of the three latest registered codes.

Data from the ICD-10 codes (data from 1997-2011) were used to identify women in the IPR and the Swedish Cancer Register to cover the diagnosis of former/current BC, EC and PE *(Table 2)*. The codes of ICD-10 were converted to ICD-9 (data from 1987-1997) by the conversion table provided by the National Board of Health and Welfare *(Table 2).* After the corresponding ICD-codes were identified they were double-checked manually both ways. Data on DVT were not included because these patients are to a large extent treated as outpatients in the Swedish healthcare system. An overview of the data collection period is presented in Figure 1.

2.3 Definitions of new versus current users of HT in relation to diagnoses.

In Sweden HT is normally dispensed for three months at a time, but prescriptions may include up to four 3-month periods, i.e. for one year. To define new (incident) users of HT a preceding wash-out period of nine months (274 days) without any dispensation was used, as described previously [27, 28]. All new users were followed over the full study period, i.e. from the time of the first dispensation on 1 April 2006 or later until 31 December 2011. To define women who had been diagnosed with BC, PE or EC and been prescribed HT at least one of the diagnoses had to be identified before the first dispensation of HT.

A woman who had at least one dispensation of HT from 1 July, 2005 until 31 March, 2006, i.e. during the 274 day long wash-out period, could either have had HT initiated before 1 July 2005 or have started during the wash-out period and was thus not included among incident users *and was defined as a current user.* Women who were diagnosed before 1 April 2006 may have used HT previously and it is therefore not possible to determine whether HT was

initiated before or after these women were diagnosed. These women were prescribed HT during the study period despite being diagnosed with BC or PE before 1 July 2005.

2.4 Statistical methods.

All data from the National Board of Health and Welfare and Statistics Sweden were delivered in a coded format in Excel-files. Data were exported and analyzed by STATA version 14 (StataCorpLP, College Station, TX, USA). Descriptive statistical methods were used, i.e. median values, proportions and relative risk for the incidence expressed with Incidence Risk Ratio (IRR) together with 95% confidence interval calculated according to Rothman (Rothman, K. J. 1986. Modern Epidemiology. Boston: Little, Brown.). Missing data for each variable were handled as lost data.

2.5 Ethics.

Data from the IPR, the Swedish Cancer register and Statistics Sweden were extracted, aggregated and coded by the National Board of Health and Welfare in order to ensure full anonymity. Data protection and encoding are kept by the National Board of Health and Welfare for at least three years or longer if required. The study protocol was approved by the Regional Ethical Review Board in Linköping, Sweden, D-no 2012/386-31.

3. Results

3.1 Demographic data.

The cohort consisted of in total 2,863,643 women. The median age (10^{th}-90^{th} percentiles) of women diagnosed with BC and/or PE and classified as current and new users of HT was 62.6 years (53-75) in current users and 57.8 years (45-74) in new users. The median

age, at first dispensation, in women classified as new users diagnosed with BC and/or PE was 60.7 years (48-77).

3.2 Participants and HT-use.

Out of the 2,863,643 women about 5.3 % (n=152,032) were dispensed HT before 1st of April 2006 and were defined as current users. Almost 3 % (n=84,264) were new users of HT, since they had been dispensed HT at least once between 1 April 2006 and 31 December 2011, but not between 1 July 2005 and 31 March 2006.

In total, 171,714 of these women had at least one of the diagnoses BC, EC and/or PE whereas 148,248 had BC and/or PE. Of these 171,714 women, 0.95% (n=1,637) were classified as current users of HT, and 0.40% (n=688) as new users of HT after diagnosed with BC, EC and/or PE (data not shown in Table 3). Out of the total cohort (n=2,863,643) less than 1.5 % of women were treated with HT after at least one of the diagnoses BC, PE and/or EC. Detailed data on HT use in women classified as current and new users with or without BC, EC and/or PE are summarized in Table 3.

The data from the registers show that despite contraindications a small proportion of women still had HT prescribed and dispensed. The probability to have HT dispensed in a woman diagnosed with PE or BC (current and new users) is about one eighth compared with the population not diagnosed with PE (IRR 0.11; 95% CI 0.10-0.12) or BC (IRR 0.12; 95% CI 0.11-0.13), but higher among women diagnosed with EC compared with the population without such a diagnose (IRR 0.43; CI 0.40-0.46). Actually 2.7% of women with EC were current users and 0.9% new users of HT.

The median number of dispensations among women who were defined as current or new users of HT but not diagnosed with any of the contraindications (BC, PE, EC) were 8.0 and 3.0 respectively. In the group of women who were current users and diagnosed with either

BC or PE the median number of dispensations were 8.0 *for both BC and PE*. In new users (with a shorter average follow up) the median number of dispensation was, for women diagnosed with BC, 3.0 and PE 2.0.

3.3 Transdermal regimens among women with PE.

In the group of women who were new users of HT and diagnosed with PE before the first dispensation (n=110) 35 women (32%) were prescribed a transdermal regimen of HT at the first dispensation compared with 13,200 women prescribed transdermal HT of in total 78,598 new users (17%) in the total population (Chi 2;$p<0.001$). At the fifth dispensation 9 out of 30 women (30%) were prescribed a transdermal regimen among women diagnosed with PE compared with 5,006 out of 33,481 women (15%) in the total population. *Concerning age, there was not a higher usage of transdermal HT in older women. The relative risk for using Transdermal HT was decreasing with increasing age (OR= 0.948 (95% c.i: 0.946-0.949).*

3.4 Specialties of the prescriber of HT.

More than half of the prescriptions were made by specialists in gynecology or gynecological oncology. About 60 percent of the first prescriptions for women (new users) diagnosed with either BC or PE (n=271/435) were made by one of these two specialties and 73% of the first prescriptions to the total population of women with HT. The fifth dispensation to cases of BC or PE, most of them representing a renewal of the prescription, was in 79% of the cases (n=100/126) prescribed by either a gynecologist or a gynecological oncologist.

4. Discussion

This register based study focused on the use of HT among women diagnosed with breast cancer and/or pulmonary embolism. The probability of being a HT user despite either BC or

PE was about one eight in comparison with women without these contraindications. We assume that HT has been prescribed after careful risk- and benefit evaluation and the women prescribed with HT have had severe hot flushes and/or sweating with a great impact on their daily life. In this observational study, based on registers, it is, however, impossible to obtain detailed information about the reason for prescribing HT.

In the group of women who were classified as current users it is not possible to determine if the HT was initiated before or after the BC, PE and/or EC diagnosis or if a long time interval had elapsed between diagnose and prescription of HT. Still, women with contraindications such as BC, PE and/or EC were prescribed HT. Regarding new users with an earlier diagnosis there is no doubt that the contraindications existed when HT was prescribed.

In the group of women diagnosed with EC a greater proportion were prescribed with HT (3.6%) compared with women diagnosed with BC (1.0%) and PE (0.9%). Perhaps the somewhat higher proportion of women with EC prescribed with HT can be explained by the fact that EC is considered a weaker contraindication than BC and PE by the prescribers [29]. The fact that fewer women with contraindications were prescribed HT than women without these contraindications seems to harmonize with the Swedish recommendations from the Medicinal Product Agency, Sweden 2004, as well as up-dated international recommendations [2, 3]. However contraindications such as BC and PE are more clearly stated as absolute compared to EC which in turn maybe explains the somewhat higher proportion of women dispended with HT in that group.

Among women with previous PE the proportion who used transdermal HT was about twice the proportion of HT users in the general population, which is in line with the beliefs that transdermal HT affects the risks for PE and DVT less than oral administration [15, 30]. However, since the incidence of PE increases with age it could be speculated that the higher

use of transdermal HT in women with PE than in the total population is also affected by a tendency to use transdermal regimens in older women.

In order to check this we matched PE-cases with controls of the same age and analysed use of transdermal HT. The results show that there is not a higher usage of transdermal HT in older women. It would have been of great interest to evaluate the HT use among all women diagnosed with VTE, i.e. not only PE but also DVT, but due to the uncertainty and low validity in the out-patient register it was deemed not possible. Data on PE were on the other hand the focus in our study because these patients are usually treated initially as in-patients in the Swedish healthcare system and therefore we expected the data from IPR to be sufficiently valid.

A somewhat lower proportion of prescriptions to women with than without contraindications were made by a specialist in gynecology or gynecological oncology (60% vs 73%). Those specialists ought to be more well-informed about absolute and relative contraindications of HT, but the findings could be a consequence of confounding by indication. Those specialists may treat a higher amount of women with contraindications of which some of them probably have more disturbing hot flushes due to e.g breast cancer treatment. A weakness is that prescribers without proven speciality in gynecology or gynecological oncology may also have another speciality or be under training to become specialists in gynecology or gynecological oncology and thus not registered as specialist in the Swedish Prescribed Drug Register. Another weakness is that we did not break down the results by type of hormones. However, all HT included were preparations used for the treatment of hot flushes in perimenopausal women, and have the same contraindications for prescription. Breaking down the results in smaller groups by types of hormones would probably have lead to too few individuals in each group. However, since transdermal preparations probably have less safety concerns in relation to thromboembolic disease [15, 30] we choose to analyse those

separately. This study is based on registers and therefore we can not state whether HT was prescribed for the indication moderate to severe hot flushes or not. Since there was a low prescription rate of HT in Sweden during this period of time we assume that the majority of prescriptions were done on the correct indication.

4.1 Conclusions

In conclusion we have found that Swedish prescribers, mainly specialists in gynecology or gynecological oncology, seem to be very well aware of the recommendations for HT-use in women with contraindications. A few women, however, are prescribed HT despite absolute and/or relative contraindications such as BC, EC or PE, possibly after careful risk- and benefit evaluation and shared consent. Women with a history of PE were prescribed transdermal HT to a larger extent than women in general in line with results from observational studies. Prospective randomized studies are needed in order to prove the assumed benefit of transdermal regimens regarding risks of PE and VTE.

Conflict of interest

The authors have no competing interests or financial disclosures.

Declarations of interest: None

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Data statement

The datasets used and analysed in the current study are available from the corresponding author on reasonable request after deidentification. Data will be available ten years following article publication by submitting a proposal to the corresponding author.

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Table 1

Hormone therapy described by ATC-codes available in Sweden in between 2005-2011.

ATC-code	**Components**	**Exceptions**
G03CA03	estradiol	low dose regimens and drugs for local vaginal treatment
G03CA57	conjugated estrogens	-
G03CX01	tibolone	-
G03FA01	norethisterone/estrogen	-
G03FA12	medroxyprogesterone/estrogen	-
G03FA15	dienogest/estrogen	-
G03FA17	drospirenone/estrogen	-
G03FB05	norethisterone/estrogen*	-
G03FB06	medroxyprogesterone/estrogen*	-
G03FB09	levonorgestrel/estrogen*	-

ATC-code; Anatomic Therapeutic Chemical classification system

*sequential preparations

Table 2:

Data from the ICD-10 codes (data from 1997-2011) were used to identify women in the IPR and the Swedish Cancer Register to cover the diagnosis of former/current BC, EC and PE.

ICD-10 Code	Diagnose
C 50.0-6, 8, 9	Malignant neoplasm of breast
D 05.0, 1, 7, 9	Carcinoma in situ of breast
C 54.0, 1, 3, 8, 9	Malignant neoplasm of corpus uteri
I 26.0, 9	Pulmonary embolism

The ICD-9 codes 174.0,1,2,3,4,5,6,8,9; 175; 182.0,1,8; 415.0,1 (data from 1987-1997) corresponded to the ICD 10 codes above.

Table 3

The number (percent) of Swedish women, at least 40 years old, using hormone therapy (HT) who are diagnosed with breast cancer (BC), and/ or pulmonary embolism (PE) in the total cohort. The women who are HT-users are defined as current or new users of HT and described in relation to BC and/or PE.

	All women	Current user of HT n (%)	New user of HT n (%)	Current or new HT-user n (%)	Incidence rate ratio (95% conf.interval)
All women (total cohort)	2,863,643	152,032 (5.31)	84,264 (2.94)	236,296 (8.25)	1
All women except women with BC and/or PE	2,715,395	151,034 (5.56)	83,775 (3.09)	234,809 (8.65)	
Women diagnosed with either BC and/or PE	148,248*	1,021 (0.69)	489 (0.33)	1,510 (1.02)	0.12 (0.11-0.13)
Women diagnosed with BC[1]	118,024	816 (0.69)	374 (0.32)	1,178 (1.00)	0.12 (0.11-0.13)
Women diagnosed with PE[2]	37,326	206 (0.55)	118 (0.32)	337 (0.90)	0.11 (0.10-0.12)
Women diagnosed with EC[3]	23,466	628 (2.68)	206 (0.88)	834 (3.55)	0.43 (0.40-0.46)

*Notify that the numbers of women with either BC or PE is lower than the sum of women diagnosed with BC and PE respectively because some women had both diagnoses.
[1]BC-diagnosis from 1987-01-01-2011-12-31
[2]PE-diagnosis from 1997-01-01-2011-12-31
[3]EC-diagnosis from 1987-01-01-2011-12-31

Figure 1: Schedule of data collection A schedule showing when data used in the study were collected from different national registers and how "new users of HT" were defined. ICD denotes International Statistical Classification of Diseases and Related Health Problems. HT denotes Hormone Therapy.