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Utilization pattern of hormone therapy in UK general practice between 1996 and 2015: a descriptive study

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Abstract

Objective: To describe the long-term trends in hormone therapy (HT) use in UK general practice after evidence of associated increased risks of cardiovascular disease (CVD) and breast cancer, subsequent guideline changes in 2003/2004 advising individualized HT prescribing, and halving of HT use between 2002 and 2005.

Methods: We conducted a descriptive study to quantify annual proportions of overall and new HT use in women aged 40 to 79 years, using the UK-based Clinical Practice Research Datalink (1996-2015). We further described HT utilization patterns (drug type, administration route, dose) within 2-year blocks overall and within subpopulations with pre-existing CVD or breast cancer.

Results: Overall HT use continued to decline from 9.4% in 2006 to 7.5% in 2015. Between 1998 and 2001, the proportion of HT initiation was around 1.7%, which halved by 2005 (0.8%), and increased again up until 2015 (1.0%). The mean age of HT users increased from 54.7 in 1996/1997 to 56.6 in 2002/2003, and leveled off at 57 to 58 years in 2014/2015. The prevalence of CVD in HT users decreased from a peak of 5.8% in 2002/2003 to 4.5% in 2014/2015, whereas breast cancer prevalence continuously increased from 0.9% in 1996/1997 to 1.9% in 2014/2015. Overall, we observed trends towards use of estrogen therapy, vaginal HT, and lower HT dose after 2002/2003, which were stronger among subpopulations with pre-existing CVD or breast cancer.

Conclusion: Our study suggests that the HT guideline changes implemented in UK clinical practice resulted in safer HT use, particularly in women with pre-existing CVD or breast cancer.

Key Words: Drug utilization – Epidemiology – Hormone therapy.

In the 1960s, synthetic hormone therapy (HT) was introduced for the treatment of postmenopausal symptoms (mainly vasomotor symptoms), and was soon seen as a remedy to preserve women's youth.[1] In addition, in the 1980s and 1990s, several observational studies reported a protective effect of HT on risk of cardiovascular diseases (CVDs), for which a causal explanation became accepted knowledge.[2-4] However, two randomized controlled trials published in the late 1990s (Heart and Estrogen/progestin Replacement Study [HERS]) and early 2000s (Women's Health Initiative [WHI]) contradicted these findings: the first reported no cardioprotective effect, and the second a slightly increased risk of CVD for oral estrogen plus progestogen (EPT, the most widely used HT).[5,6] The WHI and the Million Women Study (MWS)—a large observational study published in 2003—further reported an increased risk of breast cancer associated with oral EPT (WHI), and with any estrogen-containing therapy (ie, EPT and estrogen therapy [ET]) (MWS).[6,7] Subsequently, in 2003 and 2004, all major menopause societies (ie, The North American Menopause Society [NAMS], the International Menopause Society [IMS], and the European Menopause and Andropause Society [EMAS]) changed their guidelines on safe HT use.[8-12] They took into account all study results and provided balanced perspectives that considered study limitations (HT users were found to be systematically different from participating nonusers). Moreover, they emphasized the implications of the study findings (ie, small absolute risks: seven additional CVD cases per 10,000 women per year in the first 5 years of EPT use) rather than relative risks (ie, 29% increased CVD risk in the first 5 years of EPT use). Further, they advised individualized HT use (ie, attention to agents, administration route, dose, and length of treatment) based on important baseline risks (ie, age, lifestyle, family history of CVD, or breast cancer). Their later position papers provided further guidance on use of HT for postmenopausal symptoms by differentiating risk profiles.[13-18]

Three studies described HT use in the UK within periods between 1991 and 2010.[19-21] They found an increase in HT

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use until around 2002 and a subsequent decline until 2010.[19,20] However, none of these studies described proportion of new HT use, HT user characteristics, or use of different drug types, administration routes, or doses of HT in the general UK female population or subpopulations at high risk of first-time or recurrent CVD or breast cancer over time.

In this study, we described the long-term impact of HT use guideline changes in 2003/2004 newly advising individualized HT use based on risk profiles, by estimating overall and new HT use by year from 1996 through 2015. Furthermore, we described the impact of guideline changes on characteristics of HT users over time, and described detailed HT utilization patterns (drug types, administration routes, and estrogen doses of HT) among the general UK female population overall, and separately among subpopulations with breast cancer, CVD, or CVD risk factors.

METHODS

Study design and data source

We conducted a population-based descriptive study using data derived from Clinical Practice Research Datalink (CPRD) primary care data obtained under license from the UK Medicines and Healthcare products Regulatory Agency. Patients provide their data, which are collected by the National Health Service (NHS) as part of their care and support. The CPRD comprises this de-identified primary care data of more than 11.3 million patients.[22] General practitioners (GPs)—gatekeepers within the NHS—record information on diagnoses, prescriptions, medical symptoms, laboratory values, referrals to secondary care, demographics, and lifestyle factors (eg, BMI, smoking status) on computers.[23] Diagnoses were repeatedly shown to be of high validity.[24] We further used CPRD-linked patient-level data on Index of Multiple Deprivation (IMD), which is available for English patients only.[25,26]

The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (protocol 18_034R, made available to journal editors of this manuscript). The interpretation and conclusions contained in this study are those of the authors alone.

Study population

We identified all women aged 40 to 79 years (based on their year of birth) between January 1996 and December 2015 (study period). To capture new use of HT, we restricted the study population to women who had no HT prescriptions before age 40 (based on their year of birth), had at least 3 years of history in the database before their first HT prescription, and who had $\geq$1 GP contacts before the first HT prescription.

Exposure

We defined HT use as a recorded prescription for any ET, EPT (including separate ET and progestogen prescriptions prescribed within close proximity), or tibolone product, regardless of route of administration. We categorized estrogen doses of HT products (further referred to as ''doses'') according to a product's single estrogen dose strength (Supplement Digital Content [SDC] 1, http://links.lww.com/MENO/A384).[27-29]

Covariates

We described the following patient characteristics among HT users and nousers: mean age in years, mean number of GP contacts, IMD in quintiles where ''1 = least deprived'' and ''5 = most deprived'', a record of breast cancer, CVD (defined as myocardial infarction, ischemic stroke, or angina pectoris), and CVD risk factors (current smoking, obesity or BMI value $>30\,kg/m^2$, hypertension, hyperlipidemia, or diabetes). We identified diagnoses using Read codes.[24]

Data analysis

We divided the study period into twenty 1-year blocks, and estimated the annual proportion of overall and new HT use. Proportions were estimated by dividing the number of HT users, respectively, new HT users only in each calendar-year by the total number of women aged 40 to 79 years available in the CPRD at any time during the respective year. We further stratified proportions of new users by age groups (40-49 years, 50-59 years, 60-69 years, 70-79 years) within ten 2–year blocks (ie, 1996/1997).

Also, within each of the ten 2-year blocks in the study period, we described patient characteristics of HT users and nonusers. We further described overall and detailed HT utilization patterns in subpopulations with breast cancer, CVD, or CVD risk factors, and compared findings to those in the general UK female population (including patients with breast cancer, CVD, and CVD risk factors). Detailed HT utilization patterns comprised the following strata: drug types (ET, EPT, tibolone, mixed use), administration routes (oral, vaginal [ET only], transdermal including topical, other [injection, implant, nasal], mixed use), and doses (normal dose, low dose including ultra-low dose, mixed use) (SDC 1, http://links.lww.com/MENO/A384). ''Mixed use'' refers to concomitant or consecutive use of HT products belonging to different drug types, administration routes, or doses within any 2-year block. As HT treatment options are limited for breast cancer patients, we further described HT use by combined stratification of HT drug type, administration route, and dose. Moreover, we stratified the subpopulation with CVD risk factors by number of risk factors (0-1, 2-3, 4-5) and assessed use of HT overall and in strata of different administration routes. We calculated respective proportions in HT utilization patterns among subpopulations by dividing the number of certain HT users (eg, ET users only) in each 2-year block (given certain population restrictions, eg, CVD patients only) by the total number of women aged 40 to 79 years available in the CPRD at any time during the respective 2-year block (given certain population restrictions, eg, CVD patients only). All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

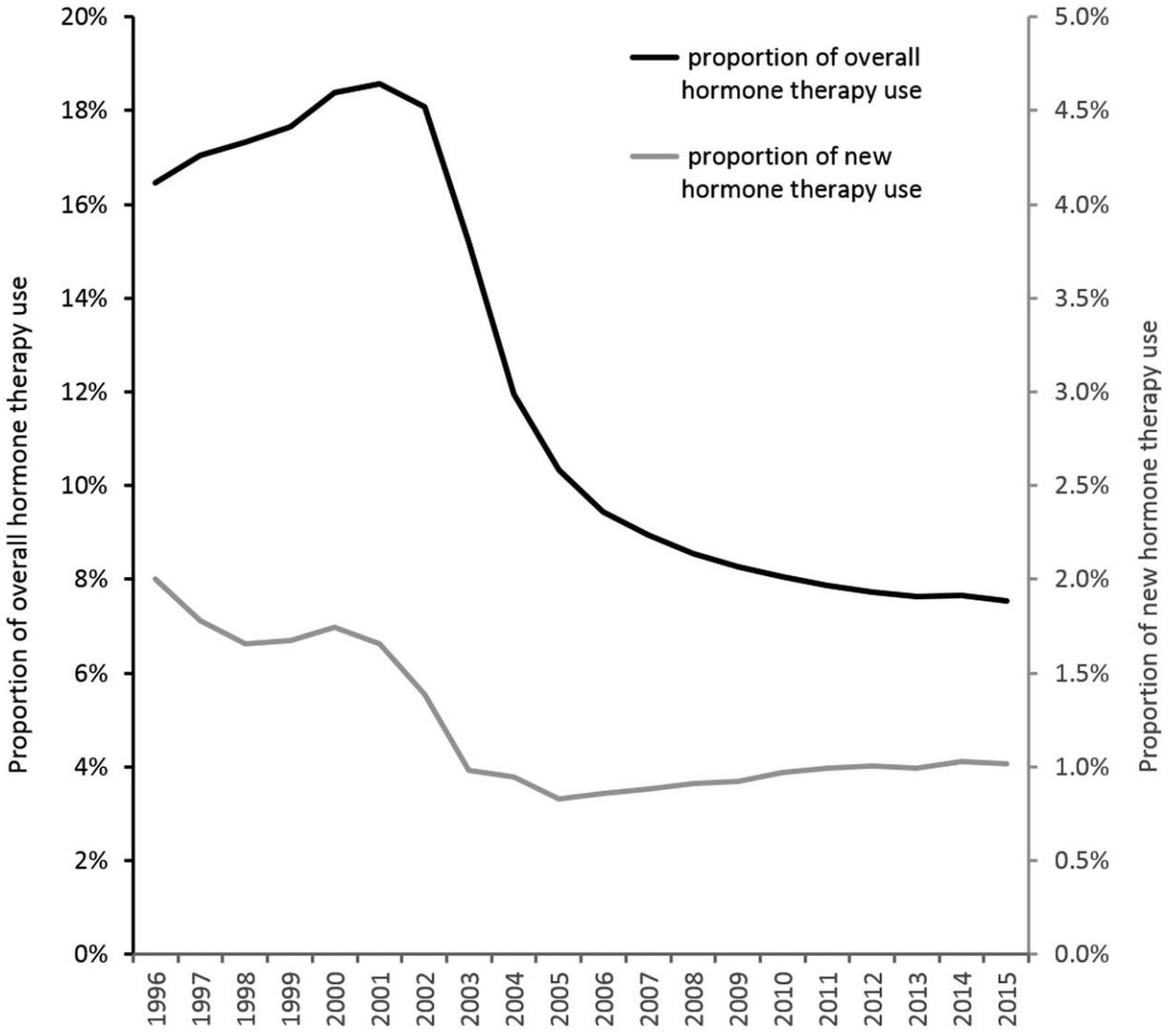

FIG. 1. Proportion of overall and new hormone therapy use in the general UK female population from 1996 to 2015. Numeric values corresponding to this figure can be found in Supplemental Digital Content 2, http://links.lww.com/MENO/A385.

RESULTS

Proportions of overall and new HT use in the general UK female population

From 1996 to 2015, among 21,218,524 women (one count for each year a woman was present), we identified 2,543,841 HT users (one count for each year a woman was prescribed HT), of whom 252,046 women met our definition of a new HT user (SDC 2, http://links.lww.com/MENO/A385). The proportion of women who received prescriptions for HT was 16.5% (142,712 HT users) in 1996, which increased to around 18% (around 195,000 HT users) between 2000 and 2002, then dropped to 10.3% (119,158 HT users) in 2005, and leveled off at 7.5% in 2015 (61,948 HT users) (Fig. 1, SDC 2, http://links.lww.com/MENO/A385). The proportion of new HT use was 2.0% (17,349 first HT prescriptions) in 1996, decreased slightly to 1.7% (17,559 first HT prescriptions) in 2001, then steeply to 0.8% (9,536 first HT prescriptions) in 2005, before slowly rising again to 1.0% (8,335 first HT prescriptions) in 2015 (Fig. 1, SDC 2, http://links.lww.com/MENO/A385). Over time, the proportion of new HT use was largest in the subgroup aged 50-59, with a maximum of 5.0% (12,363 first HT prescriptions) in 1996/1997 and a minimum of 2.3% (7,955 first HT prescriptions) in 2004/2005 (SDC 3, http://links.lww.com/MENO/A386).

Descriptive analysis of patient characteristics

Table 1 provides characteristics of HT users and nonusers over time (IMD [SDC 4, http://links.lww.com/MENO/A387]). Mean age of HT users rose from 54.7 years in 1996 to 58.7 years in 2015. Prevalence of CVD and breast cancer was lower in HT users than in nonusers throughout the study period. Mean age and prevalence of CVD and CVD risk factors converged over time in HT users and nonusers, whereas mean numbers of GP contacts and prevalence of breast cancer diverged (Graphs in SDC 5, http://links.lww.com/MENO/A388). SDC 6 (http://links.lww.com/MENO/

TABLE 1. *Main patient characteristics of hormone therapy users and nonusers from 1996/1997 to 2014/2015*

Exposure status	Years	Number of women	Mean age [y] (SD)	Mean number of GP contacts (SD)	Breast cancer (%)	CVD (%)	CVD risk factors (%)
HT users	96/97	180,034	54.7 (7.9)	21.9 (17.0)	1,633 (0.9)	9,130 (5.1)	97,189 (54.0)
	98/99	203,459	55.3 (7.9)	23.0 (17.9)	1,999 (1.0)	10,799 (5.3)	114,983 (56.5)
	00/01	226,176	55.8 (7.9)	25.2 (19.3)	2,449 (1.1)	12,449 (5.5)	135,204 (59.8)
	02/03	218,882	56.6 (7.9)	27.9 (21.2)	2,780 (1.3)	12,693 (5.8)	139,837 (63.9)
	04/05	156,313	56.9 (8.2)	32.6 (24.3)	2,380 (1.5)	8,591 (5.5)	105,207 (67.3)
	06/07	132,624	57.1 (8.5)	35.2 (26.1)	2,289 (1.7)	6,862 (5.2)	90,398 (68.2)
	08/09	120,734	57.5 (8.8)	38.4 (28.0)	2,214 (1.8)	6,050 (5.0)	82,955 (68.7)
	10/11	112,636	57.8 (8.9)	39.7 (29.1)	2,102 (1.9)	5,441 (4.8)	77,106 (68.5)
	12/13	102,821	58.1 (9.0)	41.7 (30.4)	2,066 (2.0)	4,852 (4.7)	70,899 (69.0)
	14/15	87,413	58.3 (9.0)	40.8 (31.1)	1,651 (1.9)	3,933 (4.5)	60,487 (69.2)
Nonusers	96/97	778,763	58.1 (12.2)	16.3 (16.6)	17,601 (2.3)	59,648 (7.7)	384,578 (49.4)
	98/99	842,335	57.9 (12.4)	17.4 (17.6)	20,917 (2.5)	65,566 (7.8)	436,423 (51.2)
	00/01	893,320	57.4 (12.3)	19.1 (19.3)	24,437 (2.7)	68,824 (7.7)	490,062 (54.9)
	02/03	956,980	56.9 (12.2)	20.8 (20.9)	27,893 (2.9)	70,826 (7.4)	560,143 (58.5)
	04/05	1,063,195	56.6 (11.9)	24.1 (23.3)	32,391 (3.1)	73,486 (6.9)	667,665 (62.8)
	06/07	1,120,604	56.5 (11.7)	25.9 (24.9)	35,924 (3.2)	72,602 (6.5)	730,295 (65.2)
	08/09	1,123,509	56.5 (11.6)	27.8 (26.4)	38,033 (3.4)	68,582 (6.1)	747,079 (66.5)
	10/11	1,103,173	56.5 (11.5)	28.6 (27.2)	39,339 (3.6)	63,652 (5.8)	742,856 (67.3)
	12/13	1,046,396	56.7 (11.4)	30.1 (28.4)	39,265 (3.8)	57,731 (5.5)	714,070 (68.2)
	14/15	914,804	57.1 (11.4)	29.2 (28.4)	36,164 (4.0)	49,444 (5.4)	632,296 (69.1)

Graphs corresponding to this table can be found in Supplemental Digital Content 5, http://links.lww.com/MENO/A388. Information on index of multiple deprivation distribution among HT users and nonusers is provided in Supplement Digital Content 4, http://links.lww.com/MENO/A387.
CVD, cardiovascular disease (comprises myocardial infarction, ischemic stroke, and angina pectoris); GP, general practitioner; HT, hormone therapy; SD, standard deviation.

A389) provides additional details of characteristics used to define CVD and CVD risk factors. The distribution of IMD remained stable throughout the study period. HT users were on average less deprived than nonusers; there was a higher proportion of HT users with IMD index 1 to 3 and lower proportion with an IMD index of 4 to 5 (SDC 4, http://links.lww.com/MENO/A387).

Hormone therapy utilization patterns among patients with breast cancer, CVD, and CVD risk factors

The proportions of overall HT use over time among breast cancer patients (4.4%-9.1%) and CVD patients (7.4%-15.3%) was lower than that in the general UK female population (8.7%-20.2%) (SDC 7, http://links.lww.com/MENO/A390). Detailed HT utilization patterns over time in subpopulations

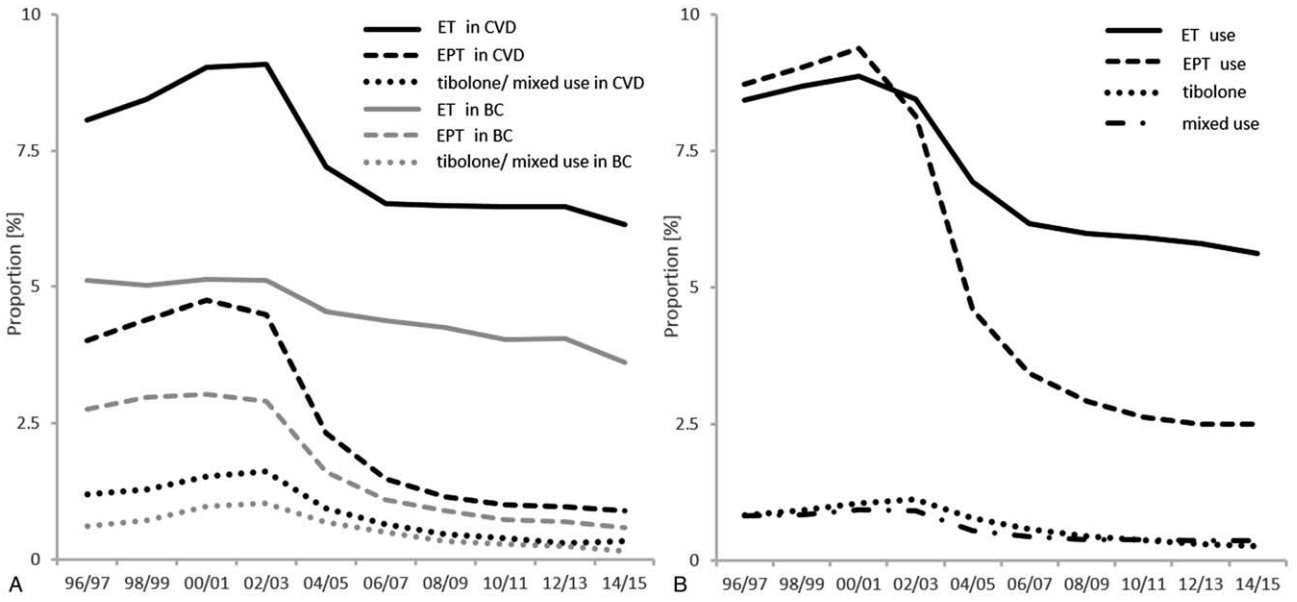

FIG. 2. Proportion of use of different hormone therapy drug types over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Numeric values corresponding to this figure can be found in Supplemental Digital Content 8, http://links.lww.com/MENO/A391. BC, breast cancer; CVD, cardiovascular disease; ET, estrogen therapy; EPT, estrogen plus progestogen therapy.

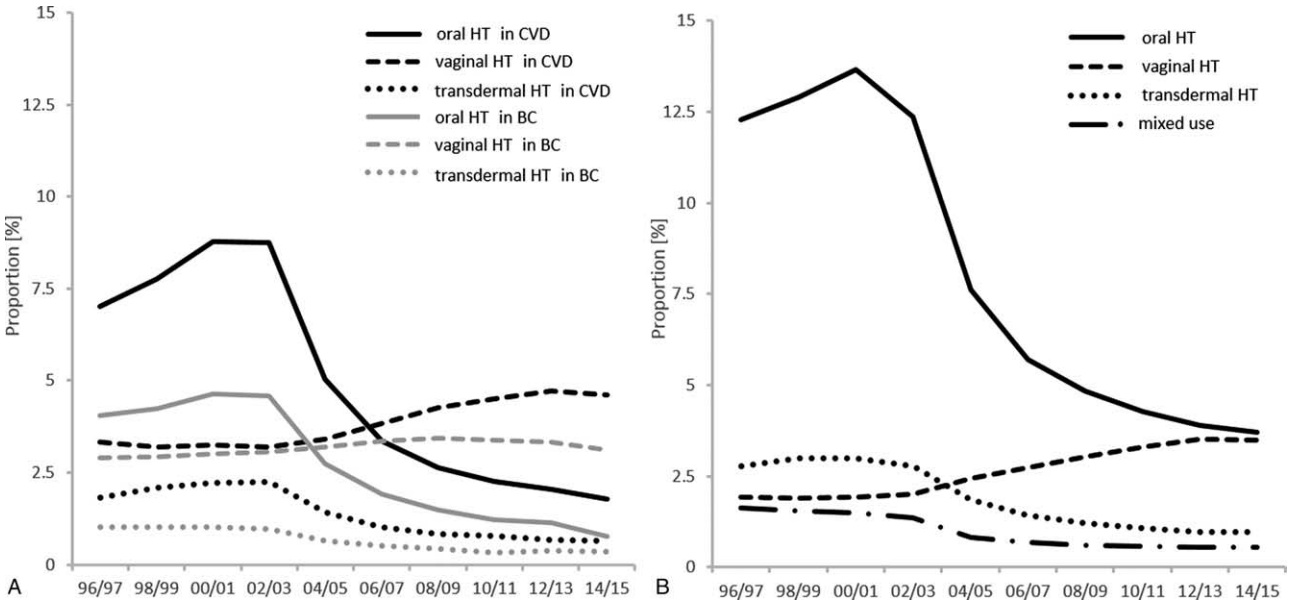

FIG. 3. Proportion of use of different hormone therapy administration routes over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Other hormone therapy/ mixed use is not shown in (**A**) as they were both negligible. Other hormone therapy use includes injections, implants, and nasal administrations. Numeric values corresponding to this figure can be found in Supplemental Digital Content 9, http://links.lww.com/MENO/A392. BC, breast cancer; CVD, cardiovascular disease; HT, hormone therapy.

with breast cancer and CVD revealed that these patients used proportionally more ET (3.6%-5.1% in breast cancer patients, 6.2%-9.1% in CVD patients) than EPT (0.6%-3.0% in breast cancer patients, 0.9%-4.8% in CVD patients) (Fig. 2, SDC 8, http://links.lww.com/MENO/A391). Use of ET in CVD patients was similar to use of ET in the general UK female population with a similar proportion in 2002/2003 (9.1% in CVD patients, 8.4% in the general UK female population) followed by a sharp decrease until 2006/2007 and a subsequent plateau at around 6% in both populations. In contrast, use of ET in breast cancer patients decreased slowly but continuously from 5.1% in 1996/1997 to 3.6% in 2014/2015.

There was a similar pattern of oral HT use over time in breast cancer and CVD patients, but proportionally many fewer HT users (around one-third in breast cancer and one half in CVD patients) compared with the proportion in the general

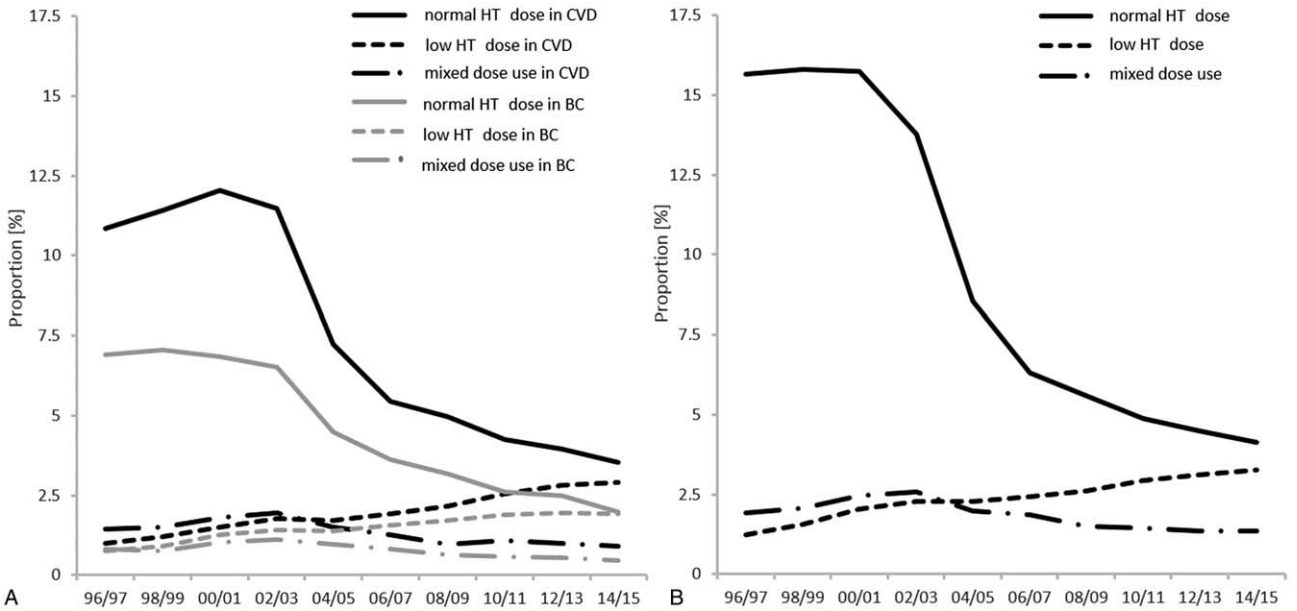

FIG. 4. Proportion of use of different hormone therapy doses over time in (**A**) the cardiovascular disease and breast cancer subpopulations; and (**B**) the general UK female population. Numeric values corresponding to this figure can be found in Supplemental Digital Content 10, http://links.lww.com/MENO/A393. BC, breast cancer; CVD, cardiovascular disease; HT, hormone therapy.

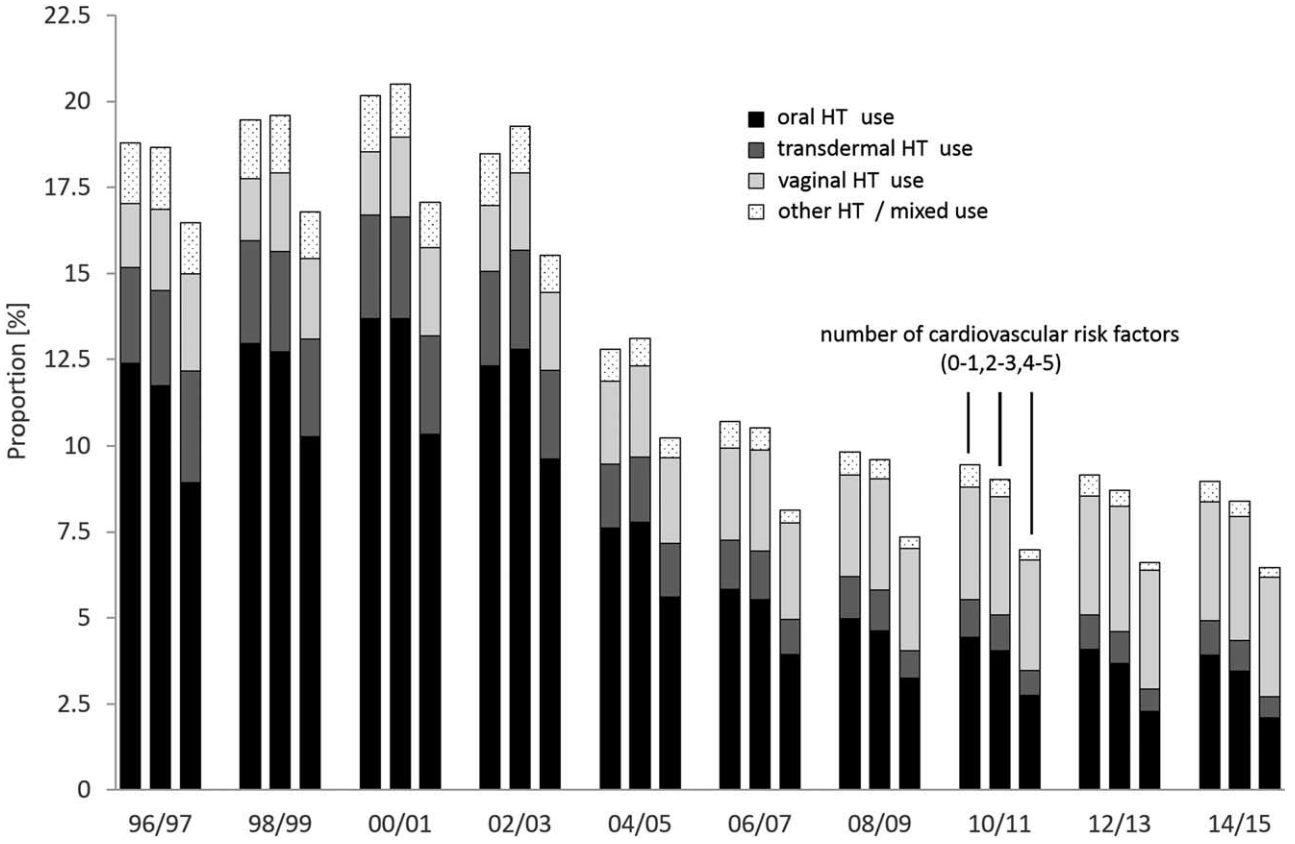

FIG. 5. Proportion of use of different hormone therapy administration routes in a subpopulation with ≥1 cardiovascular risk factor stratified by number of risk factors. Numeric values corresponding to this figure can be found in Supplemental Digital Content 13, http://links.lww.com/MENO/A396. HT, hormone therapy.

UK female population (Fig. 3, SDC 9, http://links.lww.com/MENO/A392). Furthermore, the general UK female population used predominantly oral HT in 2014/2015, closely followed by vaginal HT. In contrast, vaginal HT was used more frequently than oral HT in breast cancer patients starting in 2004/2005 and by CVD patients starting in 2006/2007 (Fig. 3, SDC 9, http://links.lww.com/MENO/A392). Use of different doses of HT was similar among the general UK female population, the breast cancer subpopulation, and the CVD subpopulation with increasing use of lower dose HT over time (Fig. 4, SDC 10, http://links.lww.com/MENO/A393). Concerning mixed use of different HT products within any 2-year block over time, there was more use of mixed HT doses (1.3%-2.6%) than use of mixed drug types (0.4%-0.8%) or administration routes (0.6%-1.6%) (Figs. 2-4, SDC 8-10, http://links.lww.com/MENO/A391-http://links.lww.com/MENO/A393). Combined stratifications of HT drug type, administration route, and dose among breast cancer patients revealed that normal dose vaginal ET steadily decreased over time (1996/1997: 2.3%, 2014/2015: 1.2%), and that low-dose vaginal ET steadily increased over time (1996/1997: 0.4%, 2014/2015: 1.6%), whereas normal-dose oral EPT and ET decreased strongly (EPT: 2.3% in 2002/2003 to 0.3% in 2014/2015, ET: 1.1% in 2002/2003 to 0.1% in 2014/2015) (SDC 11, http://links.lww.com/MENO/A394).

There was slightly more use of HT in the subpopulation of patients with CVD risk factors compared with the general UK female population at the beginning of the study period (1996/1997: 20.1% and 18.8%, respectively). However, the proportion of HT users within the two populations converged in 2014/2015 to 8.7% in both (SDC 7, http://links.lww.com/MENO/A390). Use of different drug types, administration routes, and doses of HT in patients with CVD risk factors were similar to those in the general UK female population throughout the study period (SDC 12, http://links.lww.com/MENO/A395). However, the proportion of HT use in women with 4 to 5 CVD risk factors generally decreased over time (6.5%-17.1%) and had an especially lower prevalence of oral (2.1%-10.3%) and transdermal HT use (0.6%-3.2%), when compared with women with fewer CVD risk factors (Fig. 5, SDC 13, http://links.lww.com/MENO/A396).

DISCUSSION

In this large descriptive study, we quantified the use of HT in the general UK female population, and described patient characteristics of HT users and nonusers between 1996 and 2015. We further described detailed HT utilization patterns among the general UK female population and in subpopulations with breast cancer, CVD, and CVD risk factors over time.

The overall use of HT in this study was consistent with use reported in prior studies conducted in the UK which found a slight increase in HT use from 1996 until 2001, followed by a drop until 2010.[19,20] Our study added previously unreported trends in use of HT between 2011 and 2015, which described a further decline in HT use from 7.9% in 2011 to 7.5% in 2015 in the UK. The continuous decline in the proportion of HT users from 2005 to 2015 was in contrast to the steady increase in proportions of new users of HT during this period (from 0.8% to 1.0%), indicating that duration of HT use likely decreased with time. Before 2006, we observed a 50% decline in new use of HT (from 1.7% in 2001 to 0.8% in 2005). This drop was mainly due to a decrease in new use of HT among patients less than 69 years of age. We observed a 70% decrease in use of EPT, oral HT, and normal-dose HT from 2002/2003 to 2014/2015, potential consequences of the WHI and MWS studies reporting increased CVD and breast cancer risks associated mainly with normal doses of oral EPT.[6,7] The prevalence of ET use also decreased by around 30% in this period, perhaps the result of MWS finding of an increased breast cancer risk associated with any systemic HT (ie, EPT, ET, and tibolone).[7] Furthermore, we observed increased use of vaginal and low dose HT likely as safer options for women with vasomotor symptoms (ie, low-dose HT) and genitourinary symptoms (ie, vaginal HT) requiring HT.[30-32] Use of tibolone and transdermal HT use were negligible possibly for cost reasons. While use of mixed drug types or administration routes was generally negligible early in the study period, by 2014/2015, mixed use of different HT doses was around one third that of low dose HT use and one-fourth that of normal dose use. This may indicate that patients were less likely to change drug types or routes of administration, while they were willing to change HT dose.

The characteristics of HT users changed after 2002/2003. The steep increase in mean age among HT users leveled off at 57 to 58 years, and the mean number of GP contacts increased more among HT users than nonusers potentially because of questioned safety of HT reported in the media. Notably, HT remained a treatment for women of higher socioeconomic status over time.

The prevalence of breast cancer among HT users increased steadily over time, although it was lower throughout the whole study period and its increase less steep than that of nonusers. In 2004, NAMS declared HT contraindicated in women with hormone-sensitive cancer (around 70% of breast cancer diagnoses)[33] and proposed nonhormonal treatment alternatives.[34] In later NAMS position statements,[13,14] this matter was declared as unresolved because study results about risk of progression due to HT use in breast cancer patients were inconclusive.[35,36] Estrogen-depleting treatments of breast cancer such as aromatase inhibitors and tamoxifen were reported to provoke vaginal atrophy and exacerbations of vasomotor symptoms.[37,38] Thus, in women not responding to nonhormonal treatments, low-dose vaginal ET was suggested a safe option to alleviate urogenital atrophy in a literature review.[38] This is a likely reason why we observed slightly decreasing ET use overall, due to decreasing normal-dose oral and vaginal ET use, but strongly increasing low-dose vaginal ET use, while use of normal-dose oral EPT decreased by around 85% from 2002/2003 to 2014/2015 among breast cancer patients.

The previously, increasing prevalence of CVD among HT users decreased after 2002/2003, which coincided with WHI results contesting the claims of cardioprotective effects of HT.[6,39] Considering the convergence of CVD prevalence among HT users and nonusers over time, it seems that the presence of CVD became a less important factor in the decision to prescribe HT. Throughout the whole study period, the proportion of EPT, oral, and normal-dose HT use in CVD patients was around 50% lower, whereas the proportion of vaginal HT use was around 25% higher than that in the general UK female population. This indicates that GPs prescribed HT products resulting in less systemic estrogen exposure for CVD patients. Moreover, we observed that GPs were less likely to prescribe HT with progestogen, perhaps because of the existing evidence suggesting metabolic and vascular effects of progestogen.[40,41]

At the beginning of the study period, the prevalence of CVD risk factors was slightly higher among HT users than nonusers, but converged with time in the two populations. With more than 50% of HT users and nonusers diagnosed with $\geq$1 CVD risk factor, it was not surprising that trends in HT utilization patterns in patients with CVD risk factors were similar to those of the general UK female population. However, HT utilization trends varied according to the number of CVD risk factors. While use of oral and transdermal HT decreased with increasing number of CVD risk factors, use of vaginal HT use was highest in women with $\geq$2 CVD risk factors. It is likely that use of vaginal HT in women with several CVD risk factors was considered a safer choice than systemic HT use.[30-32]

A major strength of this study is its very large patient population of >2 million women, yielding informative results even for subanalyses (eg, detailed HT utilization pattern in breast cancer patients). Additionally, as CPRD prescriptions are issued electronically by the GP, we likely captured near-complete patient prescription records, especially since treatment suggestions from specialists such as gynecologists and endocrinologists, who may treat women at high risk of adverse events, are issued by the GP for reasons of reimbursement. On the contrary, we captured HT prescriptions which we approximated as HT use, though we do not know if women actually filled the prescriptions. This may have resulted in a slight overestimation of HT use. Medication details are provided in the CPRD, which allowed us to describe HT utilization patterns by drug type, administration route, and dose. However, if two different products (eg, vaginal HT and oral HT) were prescribed during the same block, we could not easily determine whether they were used concomitantly or consecutively. In this situation, we categorized them as mixed use, possibly resulting in an overestimation of mixed use and an underestimation of single

HT use. The cross-sectional assessment of prescriptions and diagnoses further means that the time of diagnoses and prescriptions remained unknown in this study. HT had to be currently prescribed during a certain block, whereas for chronic disease diagnoses, we did not differentiate between diagnoses made during or before a block. A block was 2 years long, whereas the average observation period for HT users was around 18 years. This means that diagnoses were more likely made before a block than within a block. Last, even though we required women to have 3 years of history in the database to capture incident HT use, women may not have been true first-time HT users if they changed GP practices and had longer gaps between periods of HT use. Therefore, we may have slightly overestimated the number of new HT users.

Despite these limitations, this is, to our knowledge, the first study to describe in detail the long-term impact of guideline changes on safe HT use in 2003/2004. The study focused on time trends of HT use in the general UK female population, on patient characteristics of HT users and nonusers, and on detailed HT utilization patterns in the general UK female population, and also in subpopulations with breast cancer, CVD, and CVD risk factors.

CONCLUSIONS

This large descriptive study provides information on the use of HT in the UK following efforts of the international menopause societies to promote safe HT use after publications of the WHI and MWS results. Our study suggests that guideline changes implemented in UK clinical practice guided doctors and women towards safer HT use with shorter durations, less systemic exposure (vaginal formulations, lower doses of HT), and ET rather than EPT prescriptions, particularly among women with pre-existing CVD or breast cancer.

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