Title

Vaginal estrogen therapy use and survival in women with breast cancer: Analysis of population-based cohorts from Scotland and Wales.

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Key points

Question: Do women with breast cancer who use vaginal estrogen therapy (vaginal estrogen tablets or creams) have higher risk of breast cancer-specific mortality?

Findings: In two breast cancer cohorts, including 49,237 women, there was no evidence of an increase in early breast cancer-specific mortality with use of vaginal estrogen therapy, compared with no hormone replacement therapy use, after breast cancer diagnosis.

Meaning: These findings should provide some reassurance to clinicians prescribing vaginal estrogen therapy and support guidelines suggesting that vaginal estrogen therapy can be considered in breast cancer patients with genitourinary symptoms if non-hormonal treatments have been unsuccessful.

Abstract

Importance: Genitourinary syndrome of menopause can be treated with vaginal estrogen therapy. However, there are concerns about the safety of vaginal estrogen therapy in breast cancer patients.

Objective: To determine whether women with breast cancer who use vaginal estrogen therapy, compared with women with breast cancer who do not use hormone replacement therapy, have a higher risk of breast cancer-specific mortality.

Design: In Scotland and Wales, cohorts of women newly diagnosed with breast cancer from 2000 to 2017 were identified and followed for breast cancer-specific mortality up to 2020.

Setting: Population-based breast cancer cohorts were identified from national cancer registry records in Scotland and Wales.

Participants: Participants were women aged 40 to 79 newly diagnosed with breast cancer. Women were excluded if they had a previous cancer diagnosis (except non-melanoma skin cancer).

Exposure: Vaginal estrogen therapy (including vaginal tablets and creams) was ascertained using pharmacy dispensing records from the Prescribing Information System in Scotland and general practice prescription records in Wales.

Main Outcome and Measures: The primary outcome was time to breast cancer-specific mortality from national mortality records. Time-dependent cox regression models were used to calculate Hazard Ratios (HR) and 95% Confidence Intervals (95% CIs) for breast cancer-specific mortality comparing vaginal estrogen therapy users with hormone replacement therapy non-users adjusting for confounders including stage and grade.

Results: The two cohorts contained 49,237 breast cancer patients and included 5,795 breast cancer-specific deaths. Around 5% (2,551) of breast cancer patients used vaginal estrogen therapy after breast cancer diagnosis. In vaginal estrogen therapy users, compared with hormone replacement therapy non-users, there was no evidence of a higher risk of breast cancer-specific mortality (pooled fully adjusted HR 0.77 95% CI 0.63, 0.94).

Conclusions and Relevance: In these large population-based breast cancer cohorts, there was no evidence of increased early breast cancer-specific mortality in patients using vaginal estrogen therapy compared with patients not using hormone replacement therapy.

Introduction

Many breast cancer patients experience genitourinary syndrome of menopause[1] (such as vaginal itchiness, burning, pain with sexual activity and urinary incontinence). These symptoms may be precipitated by endocrine treatments and contribute to non-compliance to endocrine therapy[2]. Vaginal estrogen therapy is an effective treatment for genitourinary syndrome of menopause[3]. Trials have shown increased recurrence in breast cancer patients using systemic Hormone Replacement Therapy (HRT)[4]. A recent trial observed a small increase in serum estradiol with use of a vaginal estradiol tablet (10μg)[5]. There have been no large randomised controlled trials of vaginal estrogen therapy in breast cancer patients powered to investigate recurrence or mortality[6] and observational studies have been limited by small sample size[7, 8] and unavailable confounders[9]. A recent observational Danish study showed no increase in recurrence in breast cancer patients receiving vaginal estrogen therapy, apart from a subgroup receiving both vaginal estrogen therapy and aromatase inhibitors[10]. Consequently, we investigated vaginal estrogen therapy and breast cancer-specific mortality in two large breast cancer cohorts.

Methods

We utilised the Prescribing Information System (Scotland)[11] and SAIL databank (Wales)[12]. Approvals were obtained from SAIL Databank Information Governance Review Panel (Reference: 0965) and the Privacy Advisory Committee of the National Health Service National Services Scotland (number:1617–0374).

Cohorts

Population-based cohorts of women, aged 40 to 79, newly diagnosed with breast cancer (ICD code C50) were identified from cancer registries in Scotland (2010 to 2017) and Wales (2000 to 2016). Patients previously diagnosed with other invasive cancers (except non-melanoma skin cancer) were excluded.

Exposure

Medication use was ascertained from general practitioner (GP) prescribing records (Wales) or pharmacy dispensing records (Scotland). Vaginal estrogen therapy (mainly estriol creams and estradiol tablets) and systemic HRT (including estrogen or tibolone containing products) were identified based upon the British National Formulary classification[13].

Outcome

Breast cancer-specific mortality was identified from national mortality records (an underlying cause of death of C50) up to June 2019 in Scotland and June 2020 in Wales.

Covariates

Cancer registry records provided stage, grade, radiotherapy, chemotherapy, surgery and, in Scotland, hormone receptor status. Tamoxifen, aromatase inhibitor and other medication use were identified from prescribing/dispensing records. Charlson comorbidities, anaemia, and hysterectomy/oophorectomy were determined from GP diagnoses and hospital admissions in Wales and from hospital admissions alone in Scotland. Deprivation was based upon the Index of Multiple Deprivation. GP records provided smoking and BMI (Wales only).

Statistical analysis

In the primary analysis (see eFigure 1), patients were followed from 6 months after cancer diagnosis to breast cancer-specific mortality (censored on the earliest of death from other causes, end of mortality follow-up and additionally end of GP records in Wales and date of emigration in Scotland). The exposure was modelled as a single time-varying variable, with a lag of 6 months, into the following hierarchical categories: systemic HRT (with or without vaginal estrogen therapy), vaginal estrogen therapy alone and HRT non-user. Analyses were conducted by number of prescriptions and separately for higher dose vaginal estrogen therapy (considered 25µg estradiol tablets). Time-dependent cox regression models were used to calculate Hazard Ratios (HRs), and 95% Confidence Intervals (CIs), by exposure adjusting for age, year, deprivation, surgery, chemotherapy, radiotherapy, tamoxifen/aromatase inhibitor use (modelled as time varying covariates with 6 month lags), Charlson comorbidity (before diagnosis), anaemia (before diagnosis), other medication use (including statins, aspirin, metformin and oral contraceptives before diagnosis), hysterectomy/oophorectomy (anytime up to 6 months after diagnosis), cancer stage and grade. Where missing, stage and grade were imputed using

multiple imputation with chained equations. Estimates were calculated within each cohort and pooled using random effects meta-analysis models. See the eMethods for further details.

Results

The cohorts contained 49,237 breast cancer patients and 5,795 cancer-specific deaths, with medians of 8 (IQR 5-12) and 5 (IQR 3-7) years of follow-up in Wales and Scotland, respectively. Overall, 5% (2,551) of women used vaginal estrogen therapy after diagnosis and 1% (556) systemic HRT.

Patient characteristics are shown in Table 1, eTable 1 and the eResults. Table 2 shows there was no evidence of higher cancer-specific mortality in vaginal estrogen therapy users compared with HRT non-users; indeed, there was a slight reduction (pooled fully adjusted HR 0.77 95% CI 0.63, 0.94). This estimate was similar in users of 5 or more prescriptions and with higher dose therapy use.Table 3 shows that in most sensitivity analyses the associations were similar. In particular, there were no increased risks observed after restricting to women with estrogen receptor positive breast cancer, or women on aromatase inhibitors. See the eResults for further description of findings.

Discussion

In these large contemporary population-based breast cancer cohorts, there was no evidence that vaginal estrogen therapy was associated with increased risk of early breast cancer-specific mortality.

Our null finding is similar to that of a Danish study of 8,461 breast cancer patients that observed no association between vaginal estrogen therapy and cancer recurrence (adjusted HR 1.08 95% CI 0.89, 1.32). However, that study observed a 39% increase in recurrence in users of both vaginal estrogen therapy and aromatase inhibitors[10]. We did not study recurrence, but observed no evidence of an increase in cancer-specific mortality in this subgroup. A case-control study also showed no association between vaginal estrogen therapy and breast cancer recurrence (identified from GP records) in tamoxifen users but did not adjust for stage[9]. Two small cohort studies also showed no increase in cancer recurrence in breast cancer patients using vaginal estrogen therapy[7, 8] but both included fewer than 10 recurrences in the exposed group. Finally, a recent Swedish case-control study showed no increase in cancer-specific mortality in breast cancer patients using estrogen but did not distinguish between vaginal or systemic estrogen[14].

In the absence of trials of vaginal estrogen therapy in breast cancer, our findings provide some reassurance that breast cancer patients receiving vaginal estrogen therapy are not at markedly higher risk of cancer-specific mortality and would appear to support guidelines suggesting that vaginal estrogen therapy can be considered for genitourinary symptoms if non-hormonal treatments have been unsuccessful[3, 15]. The systemic HRT associations were included for completeness but should not

192 influence clinical decisions given our wide confidence intervals and the fact that
193 previous trials have observed increased risks of recurrence with systemic HRT use[4].
194
195 Strengths were the large population-based cohorts with up to 20 years of follow-up
196 with linked prescribing/dispensing records, eliminating recall bias, and capturing all
197 HRT prescriptions. However, we cannot confirm medication adherence. The duration
198 of follow-up did not allow the investigation of later cancer-specific mortality and
199 further research with extended follow-up is recommended. We adjusted for many
200 important confounders including stage and grade and, in a sensitivity analysis, BMI
201 and smoking status, but we cannot rule out residual confounding from poorly
202 recorded or unavailable variables (such as physical activity and menopausal
203 status)[3]. Estrogen receptor status of the tumor was not complete, but results were
204 similar in endocrine therapy users (who will have estrogen receptor positive
205 disease). Finally, patients receiving treatment for genitourinary syndrome of
206 menopause may have lower estradiol levels, and/or better compliance to endocrine
207 therapies, and have lower breast cancer-specific mortality anyway.
208
209 **Conclusion**
210 In summary, in this large real-world analysis, there was no evidence of increased
211 early cancer-specific mortality in breast cancer patients using vaginal estrogen
212 therapy providing some reassurance to clinicians prescribing, and patients using
213 vaginal estrogen therapy.
214

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Concept and design: Coupland, Hicks, Hughes, McMenamin, Murchie, Cardwell.

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Table 1: Patient characteristics by HRT use after diagnosis.

	Scotland			Wales		
	No HRT	Systemic HRT	Only vaginal estrogen	No HRT	Systemic HRT	Only vaginal estrogen
Age						
40-49	4207 (17%)	32 (15%)	184 (14%)	3491 (17%)	49 (14%)	184 (15%)
50-59	7444 (29%)	86 (39%)	455 (34%)	6143 (30%)	153 (45%)	411 (34%)
60-69	8231 (32%)	71 (33%)	436 (32%)	6685 (32%)	104 (31%)	394 (33%)
70-79	5506 (22%)	29 (13%)	281 (21%)	4423 (21%)	32 (9%)	206 (17%)
Year of diagnosis						
2000-2004				4795 (23%)	139 (41%)	443 (37%)
2005-2009				6030 (29%)	94 (28%)	422 (35%)
2010-2014	15674 (62%)	155(71%)	1,045(77%)	6967 (34%)	86 (25%)	270 (23%)
2015-2017	9714 (38%)	63(29%)	311(23%)	2950 (14%)	19 (6%)	60 (5%)
Deprivation						
1st fifth (most deprived)	5580 (22%)	44 (20%)	342 (25%)	3387 (16%)	70 (21%)	158 (13%)
5th fifth (least deprived)	4240 (17%)	38 (17%)	202 (15%)	4634 (22%)	73 (22%)	313 (26%)
Hysterectomy / oophorectomy[1]						
Before or at cancer diagnosis	1034 (4%)	23-28[2] (11%)	50-55[2] (4%)	1476 (7%)	41 (12%)	87 (7%)
After cancer diagnosis	740 (3%)	< 5[2]	53 (4%)	1092 (5%)	33 (10%)	110 (9%)
Select comorbidity (any time before diagnosis)						
COPD	1413 (6%)	24 (11%)	90 (7%)	781 (4%)	23 (7%)	33 (3%)
Diabetes	1760 (7%)	12 (6%)	101 (7%)	1653 (8%)	21 (6%)	77 (6%)
Chronic kidney disease	250 (1%)	< 5[2]	16 (1%)	1093 (5%)	8 (2%)	48 (4%)
Anaemia	480 (2%)	< 5[2]	33 (2%)	1135 (5%)	18 (5%)	55 (5%)
Medication use (any time before diagnosis)						
Statin	6254 (25%)	59 (27%)	361 (27%)	4920 (24%)	69 (20%)	263 (22%)
Aspirin	3742 (15%)	35 (16%)	213 (16%)	3360 (16%)	53 (16%)	174 (15%)
Metformin	1302 (5%)	8 (4%)	73 (5%)	1054 (5%)	18 (5%)	54 (5%)
Oral contraceptive	1666 (7%)	13 (6%)	83 (6%)	1841 (9%)	23 (7%)	90 (8%)
Hormone receptor status						
Estrogen receptor positive	21287 (84%)	171 (78%)	1136 (84%)			
Progesterone receptor positive	14340 (57%)	136 (62%)	706 (52%)			
HER2 receptor positive	3581 (14%)	25 (12%)	198 (15%)			
Cancer stage						
1	11150 (44%)	119 (55%)	710 (52%)	8475 (41%)	179 (53%)	554 (46%)
2	9513 (38%)	70 (32%)	490 (36%)	6812 (33%)	80 (24%)	331 (28%)
3	1903 (8%)	9 (4%)	65 (5%)	1698 (8%)	8-18[2]	45-55[2]
4	1183 (5%)	7 (3%)	21 (2%)	378 (2%)	<10[2]	<10 [2]
Missing	1639 (7%)	13 (6%)	70 (5%)	3379 (16%)	61 (18%)	255 (21%)
Cancer grade						
1	3204 (13%)	39 (18%)	214 (16%)	3120 (15%)	66 (20%)	224 (19%)
2	11899 (47%)	105 (48%)	680 (50%)	9390 (45%)	155 (46%)	535 (45%)
3	8827 (35%)	59 (27%)	406 (30%)	5205 (25%)	60 (18%)	266 (22%)
Missing	1458 (6%)	15 (7%)	56 (4%)	3027 (15%)	57 (17%)	170 (14%)
Cancer treatment						
Surgery	21257 (84%)	196 (90%)	1234 (91%)	18699 (90%)	304 (90%)	1110 (93%)
Chemotherapy	9393 (37%)	67 (31%)	465 (34%)	1500 (7%)	26 (8%)	85 (7%)
Radiotherapy	10726 (42%)	95 (44%)	650 (48%)	6030 (29%)	63 (19%)	315 (26%)
Hormonal treatment (any time after diagnosis)						
Tamoxifen	13864 (55%)	109 (50%)	725 (54%)	12721 (61%)	196 (58%)	690 (58%)
Aromatase inhibitor	12191 (48%)	115 (53%)	769 (57%)	8722 (42%)	164 (49%)	648 (54%)

[1]Hysterectomy/ oophorectomy in the following time periods: before cancer or at cancer diagnosis (anytime up to 6 months after cancer diagnosis), and after cancer diagnosis (more than 6 months after cancer diagnosis).
[2]Range shown to maintain statistical disclosure control.

Table 2: Vaginal estrogen therapy use after diagnosis and cancer-specific mortality pooled in Scotland and Wales.

Analysis	Events	Person years	Unadjusted HR (95% CI)	P	Adjusted[1] HR (95% CI)	P	Fully adjusted[2] HR (95% CI)	P
			Pooled					
No HRT use	5624	285342	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Systemic HRT use	51	3894	0.75 (0.57, 0.98)	0.038	0.90 (0.63, 1.28)	0.555	0.98 (0.68, 1.40)	0.902
Only vaginal estrogen therapy use	120	11437	0.66 (0.55, 0.80)	<0.001	0.72 (0.60, 0.86)	<0.001	0.77 (0.63, 0.94)	0.011
1-4 vaginal estrogen therapy prescriptions	105	9374	0.70 (0.58, 0.85)	<0.001	0.75 (0.62, 0.92)	0.005	0.81 (0.67, 0.99)	0.04
5+ vaginal estrogen therapy prescriptions	15	2062	0.49 (0.30, 0.82)	0.007	0.55 (0.32, 0.97)	0.04	0.57 (0.34, 0.96)	0.033
Lower dose vaginal estrogen therapy	92-97[4]	9098	0.65 (0.53, 0.80)	<0.001	0.71 (0.55, 0.93)	0.011	0.77 (0.56, 1.07)	0.122
Higher dose vaginal estrogen therapy[3]	23-28[4]	2339	0.69 (0.39, 1.21)	0.197	0.78 (0.53, 1.15)	0.215	0.81 (0.55, 1.21)	0.311
			Scotland					
No HRT use	2293	115520	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Systemic HRT use	15	859	0.91 (0.55, 1.51)	0.72	1.14 (0.69, 1.90)	0.61	1.26 (0.73, 2.16)	0.41
Only vaginal estrogen therapy use	45	3979	0.65 (0.48, 0.88)	<0.001	0.78 (0.58, 1.05)	0.1	0.88 (0.65, 1.19)	0.4
			Wales					
No HRT use	3331	169822	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
Systemic HRT use	36	3035	0.69 (0.49, 0.95)	0.025	0.78 (0.56, 1.09)	0.145	0.86 (0.61, 1.21)	0.383
Only vaginal estrogen therapy use	75	7458	0.67 (0.53, 0.85)	0.001	0.68 (0.54, 0.86)	0.001	0.71 (0.56, 0.90)	0.005

[1]Adjusted model for age, year, deprivation, cancer treatment (surgery, radio, chemo), tamoxifen (as time varying covariate), aromatase inhibitors (as time varying covariate), Charlson comorbidities (before diagnosis), anaemia (before diagnosis), medication use (before diagnosis: statin, aspirin, metformin, oral contraceptives) and hysterectomy/oophorectomy (before or at diagnosis).[2]Model contains variables in [1] and stage and grade using multiple imputation. [3]Higher dose vaginal estrogen therapy contains 25µg estradiol tablets and lower dose consists of all other vaginal estrogen therapy. [4]Range shown to maintain statistical disclosure control.

Table 3: Sensitivity analyses for the association between vaginal estrogen therapy use compared with no HRT use after cancer diagnosis.

Analysis	Non-user events (person years)	Vaginal estrogen events (person years)	Unadjusted HR (95% CI)	Adjusted[1] HR (95% CI)	Fully adjusted[2] HR (95%CI)
Main analysis	5624 (285342)	120 (11437)	0.66 (0.55, 0.80)	0.72 (0.60, 0.86)	0.77 (0.63, 0.94)
Using 1 year lag	5132 (262441)	104 (10202)	0.67 (0.55, 0.81)	0.72 (0.59, 0.87)	0.77 (0.63, 0.94)
Using 2 year lag	3932 (218204)	76 (8046)	0.63 (0.42, 0.95)	0.72 (0.57, 0.90)	0.75 (0.60, 0.95)
Restricted to age 55 to 79 years at diagnosis	3880 (187722)	86 (7745)	0.67 (0.54, 0.83)	0.76 (0.61, 0.95)	0.82 (0.63, 1.07)
Including age 18 to 79 years at diagnosis	6062 (299018)	121 (11725)	0.64 (0.53, 0.77)	0.69 (0.57, 0.82)	0.74 (0.61, 0.90)
Restricted to stage 1 to 3	3551 (243892)	90 (9329)	0.73 (0.59, 0.90)	0.75 (0.60, 0.92)	0.80 (0.65, 0.99)
New HRT users[3]	5046 (233546)	68 (6572)	0.66 (0.52, 0.84)	0.70 (0.55, 0.90)	0.76 (0.59, 0.97)
Adjusting for prior HRT use	5624 (285342)	120 (11437)	0.66 (0.55, 0.80)	0.77 (0.64, 0.92)	0.81 (0.67, 0.98)
Estrogen receptor positive breast cancer[4]	1516 (98591)	35 (3366)	0.69 (0.49, 0.97)	0.83 (0.59, 1.16)	0.88 (0.62, 1.25)
Estrogen receptor negative breast cancer[4]	732 (15438)	10 (579)	0.53 (0.28, 0.98)	0.55 (0.29, 1.03)	0.68 (0.36, 1.28)
Stratifying entire cohort[5]					
No tamoxifen or aromatase inhibitor use	1752 (60805)	21 (2207)	0.51 (0.33, 0.78)	0.56 (0.36, 0.86)	0.67 (0.43, 1.04)
Tamoxifen only use	595 (88062)	14 (3433)	0.86 (0.51, 1.48)	0.89 (0.52, 1.53)	1.01 (0.52, 1.95)
Aromatase inhibitor use (with or without tamoxifen)	3277 (136474)	85 (5797)	0.68 (0.54, 0.84)	0.70 (0.57, 0.87)	0.72 (0.58, 0.91)
Stratifying only vaginal estrogen therapy users[6]					
No tamoxifen or aromatase inhibitor use	5624 (285342)	21 (2207)	0.61 (0.37, 1.01)	0.58 (0.36, 0.94)	0.68 (0.35, 1.33)
Tamoxifen only use	5624 (285342)	14 (3433)	0.26 (0.15, 0.43)	0.33 (0.20, 0.56)	0.41 (0.21, 0.79)
Aromatase inhibitor use (with or without tamoxifen)	5624 (285342)	85 (5797)	0.94 (0.76, 1.17)	0.98 (0.79, 1.22)	0.99 (0.79, 1.24)
Adjusting for stage and grade (complete case)[7]	3788 (231575)	88 (8886)	0.71 (0.54, 0.93)	0.72 (0.54, 0.94)	0.82 (0.66, 1.01)
Additionally adjusting for smoking and BMI (multiple imputation)[7]	3331 (169822)	75 (7458)	0.67 (0.53, 0.85)	0.68 (0.54, 0.86)	0.73 (0.57, 0.92)
Breast cancer as any cause of death	6489 (285342)	144 (11437)	0.68 (0.58, 0.80)	0.73 (0.62, 0.86)	0.77 (0.65, 0.92)
Cardiovascular death	919 (285342)	42-47 (11437)	0.80 (0.30, 2.11)	0.77 (0.28, 2.15)	0.78 (0.28, 2.16)
All-cause mortality	9612 (285342)	290 (11437)	0.73 (0.58, 0.91)	0.78 (0.69, 0.88)	0.80 (0.71, 0.90)

[1]Adjusted model contains, except where otherwise stated, age, year, deprivation, cancer treatment (surgery, radio, chemo), tamoxifen (as time varying covariate), aromatase inhibitors (as time varying covariate), Charlson comorbidities (before diagnosis), anaemia (before diagnosis), medication use (before diagnosis: statin, aspirin, metformin, oral contraceptives) and

hysterectomy/oophorectomy (anytime before or up to 6 months after diagnosis). [2]Fully adjusted model contains, except where otherwise stated, variables in [1] and stage and grade using multiple imputation. [3]Restricted to individuals not using HRT before breast cancer diagnosis. [4]Scotland only. [5]Statifying entire cohort by endocrine therapy use e.g. vaginal estrogen therapy users not on tamoxifen or aromatase inhibitor are compared with HRT non-users not on tamoxifen or aromatase inhibitors. [6]Stratifying only vaginal estrogen therapy users by endocrine therapy use and hence the comparison group is all HRT non-users in each analysis e.g. vaginal estrogen therapy users not on tamoxifen or aromatase inhibitor compared with all HRT non-users. [7]Wales only.

Supplementary Online Content

McVicker L, Labeit AM, Coupland C, Hicks B, Hughes C, McMenamin Ú, McIntosh SA, Murchie P, Cardwell CR. Vaginal estrogen therapy use and survival in women with breast cancer: Analysis of population-based cohorts from Scotland and Wales.

eMethods

The study is based upon the Scottish National Prescribing Information System (Scotland)[1] and the SAIL databank (Wales)[2].

Cohorts

Population-based cohorts of females, aged 40 to 79, newly diagnosed with breast cancer (ICD code C50) were identified from cancer registry records between 2010 to 2017 in Scotland (Scottish Cancer Registry) and 2000 to 2016 in Wales (Welsh Cancer Intelligence and Surveillance Unit). Patients previously diagnosed with other invasive cancer diagnoses (apart from non-melanoma skin cancer) were excluded.

Exposure

HRT use was ascertained from electronic general practitioner (GP) prescribing records (Wales) or dispensing records (Scotland). Systemic HRT was based upon estrogen (and tibolone) containing products used for menopausal symptoms based upon the British National Formulary[3] classification (Section 6.8.1). Vaginal estrogen therapy (mainly estriol creams and estradiol vaginal tablets) was based upon the British National Formulary classification (Section 7.6.2).

Outcome

The primary outcome was breast cancer-specific mortality from national mortality records (based upon C50 as the underlying cause of death), available up to June 2019 in Scotland and June 2020 in Wales.

Covariates

Cancer treatment (including radiotherapy, chemotherapy and surgery) was determined from cancer registry records in Scotland and Wales. Tamoxifen and aromatase inhibitor use was taken from GP prescribing (Wales) or dispensing records (Scotland). Cancer registry records provided stage, grade and hormone receptor status (only available in Scotland). Charlson comorbidities (including myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, hemiplegia, dementia, liver diseases, peptic ulcer, chronic obstructive pulmonary disease, diabetes and chronic kidney disease) and anaemia were determined before cancer diagnosis from GP records and hospital admissions in Wales and from hospital admissions alone in Scotland (other than diabetes which was also identified from dispensed diabetes medications). Other medication use (including aspirin, statins, metformin and oral contraceptives) was determined at any time before diagnosis from GP prescribing (Wales) or dispensing records (Scotland). Hysterectomy/oophorectomy was determined from hospital admissions in Scotland and hospital admissions and GP records in Wales. Deprivation of home address was based upon the 2009 and 2011 Index of Multiple Deprivation in Scotland and Wales[1, 2], respectively. Smoking and BMI were determined from GP records (not available in Scotland).

Statistical analysis

In the primary analysis of vaginal estrogen therapy (described in Supplementary eFigure 1), patients were followed from 6 months after cancer diagnosis to breast cancer-specific mortality (censored on death from other causes, end of mortality follow-up and additionally end of GP records in Wales and date of emigration in Scotland). Consequently, patients who died in the first 6 months after cancer diagnosis were excluded as it seemed unlikely that HRT use after diagnosis could impact such deaths (in sensitivity analyses this duration was altered). Exposure was modelled as a single time-varying variable[4], with a lag[5] of 6 months, into the following hierarchical categories: systemic HRT use (with or without vaginal estrogen), vaginal estrogen therapy only use and HRT non-use, i.e. patients were considered initially non-users (unexposed) from cancer diagnosis and were considered exposed to vaginal estrogen therapy after a lag of 6 months following their first vaginal estrogen therapy prescription and were considered exposed to systemic HRT after a lag of 6 months following their first systemic HRT prescription (regardless of vaginal estrogen therapy use). An analysis was conducted by number of vaginal estrogen prescriptions with individuals considered a non-user prior to 6 months after their first prescription, a short-term user from 6 months after their first prescription to 6 months after their 5th prescription, and a longer term user after this time. A separate analysis was conducted investigating higher dose vaginal estrogen products which was restricted to vaginal estrogen therapy users who used vaginal tablets containing 25µg or more of estradiol. Time-dependent cox regression models (with time from breast cancer diagnosis as the underlying time scale) were used to calculate Hazard Ratios (HRs), and 95% Confidence Intervals (CIs), by exposure from 6 months after cancer diagnosis adjusting for age (as continuous), year of diagnosis (as continuous), deprivation, cancer treatment (including surgery, chemotherapy and radiotherapy), tamoxifen and aromatase inhibitor user (both modelled as time varying covariates with a 6 month lag), Charlson comorbidity (before diagnosis, modelling each condition separately), anaemia (before diagnosis), other medication use (including statins, aspirin, metformin and oral contraceptives before diagnosis), and hysterectomy/oophorectomy (anytime before diagnosis up to 6 months after cancer diagnosis). The Cox PH

assumption was checked by visual inspection of log(−log) plots and appeared to be largely satisfied. The main analyses were repeated adjusting for stage and grade using multiple imputation. Stage and grade were imputed using chained equations with ordered logistic regression models with cancer-specific death status, cumulative hazard and other confounders (including age, year, deprivation, cancer treatment, comorbidity, other medication use and hysterectomy/oophorectomy) in imputation models[6]. Twenty datasets were imputed in Scotland and 10 in Wales (with a total of 200 iterations performed in Scotland and 100 in Wales) and results were combined using Rubin's rules. Imputation was implemented using STATA's mi impute routine. Estimates were calculated within each cohort and then pooled using random effects meta-analysis models[7].

Various sensitivity analyses were conducted. First, the lag was increased to one year and two years (with follow-up starting at one year and two years after cancer diagnosis respectively). Second, analyses were conducted varying the age at diagnosis range: restricting to women over 55 years (probably post-menopausal), and widening to women 18 to 79 years. Third, an analysis was conducted restricted to patients with stage 1 to 3 disease. Fourth, to account for prior use, a new user analysis was conducted restricted to women who had no record of HRT use before breast cancer diagnosis and a separate analysis was conducted adjusting for vaginal estrogen therapy and systemic HRT use before diagnosis. Fifth, an analysis was conducted stratifying by ER status (in Scotland only). Sixth, an analysis was conducted stratifying the cohort by endocrine therapy use and comparing vaginal estrogen therapy users with HRT non-users within the following strata: tamoxifen and aromatase inhibitor non-users, tamoxifen only users (without aromatase inhibitors), and aromatase inhibitor users (with or without tamoxifen use); based upon use of aromatase inhibitor and tamoxifen as time varying covariates lagged by 6 months. To allow comparison with an earlier study[8], this analysis was repeated stratifying only the vaginal estrogen therapy users e.g. vaginal estrogen therapy users not on tamoxifen or aromatase inhibitors were compared with all HRT non-users. Seventh, an analysis was conducted adjusting for stage and grade (as a complete case analysis). Eighth, an analysis was conducted adjusting for smoking status and BMI (in Wales only, using multiple imputation). Ninth, an analysis was conducted on breast cancer-specific mortality based upon breast cancer anywhere on the death certificate. Finally, analyses were conducted on the outcome of all-cause mortality and cardiovascular death (based upon ICD10 codes I20 to I99 or G45 as the underlying cause of death). STATA 16/17 was used for all analyses.

eResults

Patient Characteristics

In the Scottish cohort, after breast cancer diagnosis, 25,388 patients did not use any HRT, 218 used systemic HRT and 1,356 used vaginal estrogen therapy (with 735 [54%] using vaginal tablets alone, 448 [33%] using vaginal creams alone, 145 [11%] using vaginal tablets and creams, and 28 [2%] using vaginal rings). In the Welsh cohort, after breast cancer diagnosis, 20,742 patients did not use any HRT, 338 used systemic HRT and 1,195 used vaginal estrogen therapy (with 383 [32%] using vaginal tablets alone, 661 [55%] using vaginal creams alone, 142-151 [12-13%] using vaginal tablets and creams, and <10 [<1%] using vaginal rings).

Patient characteristics are shown in Table 1. Many characteristics of vaginal estrogen therapy users were similar to HRT non-users including age, deprivation, comorbidities, medication use, hysterectomy/oophorectomy, hormone receptor status and tamoxifen use. For instance, in Scotland, 22% of the HRT non-users were aged 70 to 79 years and 21% of vaginal estrogen therapy users were aged 70 to 79 years. Similarly, in Scotland, 4% of HRT non-users had a hysterectomy/oophorectomy before or at diagnosis, compared with 4% of vaginal estrogen therapy users. Also, in Scotland, 25% of HRT non-users had recorded use of a statin before diagnosis compared with 27% of vaginal estrogen therapy users. However, there were some differences as vaginal estrogen therapy users, compared with HRT non-users, had slightly lower stage and grade, were more likely to have had surgery, use aromatase inhibitors and less likely to smoke. For example, in Scotland, 84% of HRT non-users had surgery compared with 91% of vaginal estrogen therapy users.

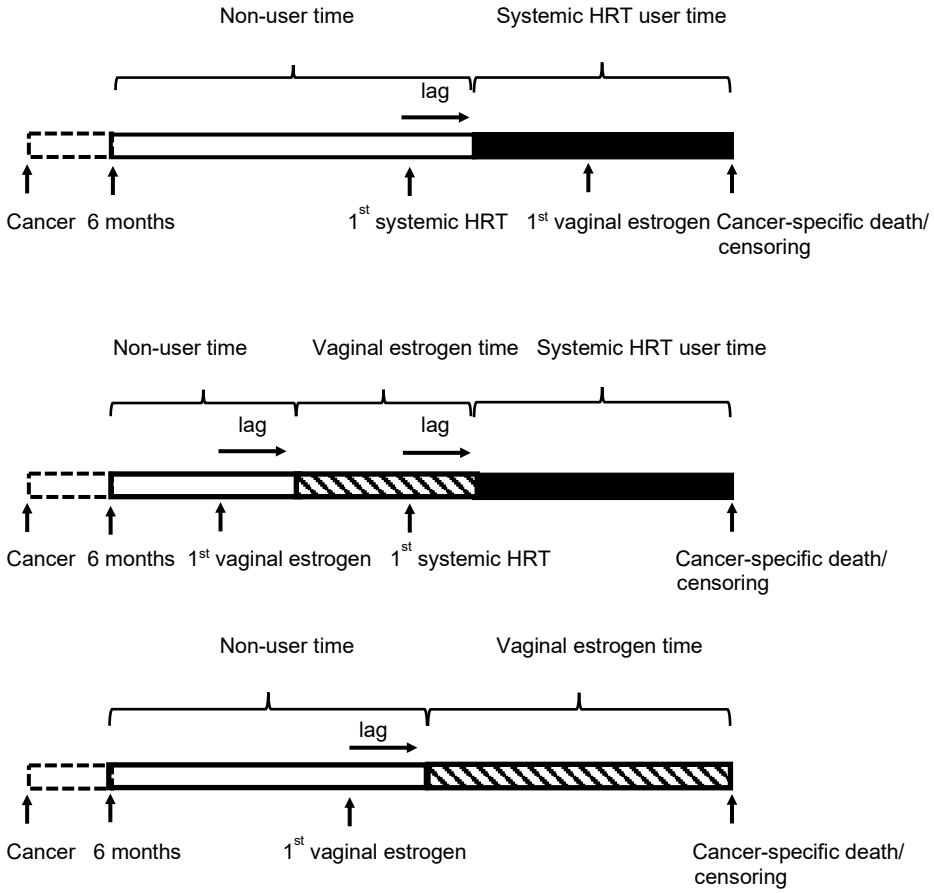
Sensitivity Analyses

Sensitivity analyses are contained in Table 3. Our main finding of no evidence of higher cancer-specific mortality in vaginal estrogen therapy users compared with HRT non-users (pooled fully adjusted HR 0.77 95% CI 0.63, 0.94) was similar when varying the lag duration, when varying the included age range, when restricting to early stage disease and or adjusting for HRT use before diagnosis. The observed association was also similar when investigating new vaginal estrogen therapy use after breast cancer diagnosis (fully adjusted HR 0.76 95% CI 0.59, 0.97). The observed estimate was slightly increased after restricting to women with estrogen receptor positive breast cancer (fully adjusted HR 0.88 95% CI 0.62, 1.25). Table 3 also shows associations by use of endocrine therapy. For instance, there was no evidence of an increase in cancer-specific mortality when comparing vaginal estrogen therapy users on aromatase inhibitors with HRT non-users on aromatase inhibitors (pooled fully adjusted HR 0.72 95% CI 0.58, 0.91), or when comparing vaginal estrogen therapy users on aromatase inhibitors with all HRT non-users (pooled fully adjusted HR 0.99 95% CI 0.79, 1.24), allowing more direct comparison with an earlier study[8]. A null association was observed when adjusting for stage and grade using a complete case approach (pooled fully adjusted HR 0.82 95% CI 0.66, 1.01). Also, the association was similar after additionally adjusting for smoking and BMI (pooled fully adjusted HR 0.73 95% CI 0.57, 0.92). The findings were also similar when breast cancer-specific death was based upon a breast cancer code anywhere on the death certificate. Finally, there was also no association between vaginal estrogen therapy and all-cause mortality (pooled fully adjusted HR 0.80 95% CI 0.71, 0.90) or cardiovascular mortality (pooled fully adjusted HR 0.78 95% CI 0.28, 2.16).

eTable 1: Additional patient characteristics by HRT use after diagnosis in patients.

	Scotland			Wales		
	No HRT	Systemic HRT	Only vaginal estrogen	No HRT	Systemic HRT	Only vaginal estrogen
Smoking						
Never				9773 (47%)	132 (39%)	545 (46%)
Ex				3947 (19%)	49 (14%)	238 (20%)
Current				3400 (16%)	58 (17%)	108 (9%)
Missing				3622 (17%)	99 (29%)	304 (25%)
BMI :n				14,558	207	753
mean (sd)				28.5 (6.1)	27.5 (5.8)	27.5 (5.4)
Comorbidity (any time before diagnosis)						
Myocardial infarction	416 (2%)	< 5	27 (2%)	304 (1%)	<5	13 (1%)
Congestive heart failure	265 (1%)	< 5	18 (1%)	321 (2%)	<5	10 (1%)
Peripheral vascular disease	240 (1%)	< 5	13 (1%)	381 (2%)	10 (3%)	20 (2%)
Stroke	307 (1%)	< 5	13 (1%)	517 (2%)	9 (3%)	15 (1%)
Hemiplegia	87 (<1%)	< 5	< 5 (<1%)	137 (1%)	<5	12 (1%)
Dementia	67 (<1%)	< 5	0 (<1%)	119 (1%)	<5	<5 (<1%)
Liver diseases	237 (1%)	< 5	10 (1%)	224 (1%)	<5	6 (1%)
Peptic ulcer	303 (1%)	< 5	16 (1%)	328 (2%)	7 (2%)	21 (2%)

eFigure 1. Figure illustrating the study design for the main analysis of vaginal estrogen.



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