Vaginal estrogen therapy use and survival in females with breast cancer

McVicker, L., Labeit, A. M., Coupland, C. A. C., Hicks, B., Hughes, C., McMenamin, Ú., McIntosh, S. A., Murchie, P., & Cardwell, C. R. (2023). Vaginal estrogen therapy use and survival in females with breast cancer. *JAMA Oncology*. Advance online publication. https://doi.org/10.1001/jamaoncol.2023.4508

Published in:
JAMA Oncology

Document Version:
Peer reviewed version

Title

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

Authors

Lauren McVicker PhD[1], Alexander M Labeit PhD[1], Carol AC Coupland PhD[2,3], Blánaid Hicks PhD[1], Carmel Hughes PhD[4], Úna McMenamin PhD [1], Stuart A McIntosh PhD[5,6], Peter Murchie MD[7], Chris R Cardwell PhD[1].

Affiliations

[1]Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland.

[2]Centre for Academic Primary Care, School of Medicine, University of Nottingham, Nottingham, UK.

[3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.

[4]School of Pharmacy, Queen's University Belfast, Belfast, Northern Ireland.

[5]The Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, Northern Ireland.

[6]Breast Surgery Department, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK.

[7]Division of Applied Health Sciences Section, Academic Primary Care, Foresterhill, Aberdeen, UK.

Author for correspondence

Prof Chris Cardwell, Queen's University Belfast, Centre for Public Health, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA. Email: c.cardwell@qub.ac.uk.

Date of revision: 28 July 2023.

Word count: 1200

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

Acknowledgement

Author contributions: Chris R Cardwell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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

Acquisition, analysis and interpretation of data: McVicker, Labeit, Coupland, Hicks, Hughes, McMenamin, McIntosh, Murchie, Cardwell.

Drafting of the manuscript: Cardwell.

Critical revision of the manuscript for important intellectual content: McVicker, Labeit, Coupland, Hicks, Hughes, McMenamin, McIntosh, Murchie, Cardwell.

Statistical analysis: Cardwell, McVicker, Labeit.

Obtaining funding: Mc Menamin, McVicker, Labeit.

Administrative, technical, or material support: None.

Supervision: None.

Other: None.

Conflict of interest disclosures: SMcI reports institutional funding for honoraria from Roche, MSD and AstraZeneca, for advisory boards from Roche, Lily and MSD, for talks from Roche and MSD, and research funding from Novartis. SMcI also reports personal funding for talks from BD Bard and conference travel and support from Roche and Lilly. The remaining authors declare they have no relevant financial or non-financial interests.

Funding/Support: This work was supported by funding from Cancer Research UK (reference C37316/A29656 and C53788/A20100) that provided access to the datasets.

Role of the Funder/Sponsor: The funding sources were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Additional Contributions: We would like to acknowledge the support of the eDRIS team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the secure analytical platform within the National Safe Haven. We would also like to acknowledge support of SAIL Databank for facilitating access to the dataset from Wales. The authors would also like to thank the PPI representatives for providing a patient and public perspective on the study design, findings, interpretation of the study and lay summary materials.

Disclaimer: None.

References

1. Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on womens midlife health and menopause hormone therapy. *Climacteric*. 2016;19:109-150.

2. Sousa MS, Peate M, Jarvis S, Hickey M, Friedlander M. A clinical guide to the management of genitourinary symptoms in breast cancer survivors on endocrine therapy. *Ther Adv Med Oncol*. 2017;9(4):269-285.

3. “The 2022 hormone therapy position statement of The North American Menopause Society” Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794.

4. Poggio F, Del Mastro L, Bruzzone M, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2022;191(2):269-275.

5. Mitchell CM, Larson JC, Crandall CJ, et al. Association of vaginal estradiol tablet with serum estrogen levels in women who are postmenopausal: Secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2022;5(11):e2241743.

6. Biglia N, Bounous VE, D'Alonzo M, et al. Vaginal atrophy in breast cancer survivors: Attitude and approaches among oncologists. *Clin Breast Cancer*. 2017;17(8):611-617.

7. Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric*. 2003;6(1):45-52.

8. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst*. 2001;93(10):754-762.

9. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. *Breast Cancer Res Treat*. 2012;135(2):603-609.

10. Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or vaginal hormone therapy after early breast cancer: A Danish observational cohort study. *J Natl Cancer Inst*. 2022 ;114(10):1347-1354.

11. Alvarez-Madrazo S, McTaggart S, Nangle C, Nicholson E, Bennie M. Data Resource Profile: The Scottish National Prescribing Information System (PIS). *Int J Epidemiol*. 2016;45(3):714-715f.

12. Ford DV, Jones KH, Verplancke JP, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res*. 2009;9:157.

13. Joint Formulary Committee. British National Formulary 80: September 2020-March 2021. (BMJ Group and Pharmaceutical Press: London, UK, 2020).

14. Sund M, Garmo H, Andersson A, Margolin S, Ahlgren J, Valachis A. Estrogen therapy after breast cancer diagnosis and breast cancer mortality risk. *Breast Cancer Res Treat*. 2023. (doi.org/10.1007/s10549-023-06871-w).

15. American College of Obstetricians and Gynecologists' Committee on Clinical Consensus-Gynecology. Treatment of urogenital symptoms in individuals with a history of estrogen-dependent breast cancer: Clinical consensus. *Obstet Gynecol*. 2021;138(6):950-960.

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.