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Title

Can demographic, clinical and treatment-related factors available at hormonal therapy initiation predict non-persistence in women with stage I-III breast cancer?

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Running Title

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Abstract (250 words)

Purpose: To investigate whether demographic, clinical and treatment-related risk factors known at treatment initiation can be used to reliably predict future hormonal therapy non-persistence in women with breast cancer, to inform intervention development.

Methods: Women with stage I-III breast cancer diagnosed 2000-2012 and prescribed hormonal therapy were identified from the National Cancer Registry Ireland (NCRI) and linked to pharmacy claims data from Ireland's Primary Care Reimbursement Services (PCRS). Non-persistence was defined as a treatment gap of ≥180 days within 5 years of initiation. Seventeen demographic, clinical and treatment-related risk factors, identified from a systematic review, were abstracted from the NCRI-PCRS dataset. Multivariate binomial models were used to estimate relative risks (RR) and risk differences (RD) for associations between risk factors and non-persistence. Calibration and discriminative performance of the models were assessed. The analysis was repeated for early non-persistence (<1 year of initiation).

Results: Within 5 years of treatment initiation 680 women (19.9%) were non-persistent. Women aged <50 years (adjusted RR 1.41, 95%CI 1.16-1.70) and those prescribed antidepressants (RR 1.22, 95%CI 1.04-1.45) had increased risk of non-persistence. Married women (RR 0.82 95%CI 0.71-0.94) and those with prior medication use (RR 0.62 95%CI 0.51-0.75) had reduced risk of non-persistence. The area under the receiver-operating characteristic (ROC) curve for non-persistence was 0.61. Findings were similar for early non-persistence.

Conclusion: The risk prediction model did not discriminate well between women at higher and lower-risk of non-persistence at treatment initiation. Future studies should consider other factors, such as psychological characteristics and experience of side-effects.

Introduction

Clinical guidelines recommend that women with hormone receptor positive breast cancer receive at least five, and up to 10, years of adjuvant hormonal therapy as a preventative measure for breast cancer recurrence and mortality.(1, 2) Reduced hormonal therapy exposure in women with breast cancer, due to either early treatment discontinuation (non-persistence) or failure to take the correct dosage at the prescribed frequency (non-adherence), has been shown to be associated with an increased risk of early breast cancer recurrence and mortality.(3-5) Despite clear clinical efficacy, non-persistence and non-adherence are both common. Rates of non-persistence at 5 years range from 16% to 32% in clinical trials of hormonal treatment and between 31% and 73% in routine clinical settings, while prevalence of non-adherence ranges from 41% to 72%.(6, 7)

Despite the high prevalence of hormonal therapy non-adherence and non-persistence, the risk factors associated with hormonal therapy medication taking behaviour (MTB) have not been established. Recent systematic reviews have identified extremes of age (i.e. older and younger), follow-up care with a general practitioner (compared to follow-up by an oncologist) and experience of treatment side-effects as largely negatively associated with persistence, while taking more medications at baseline has been positively associated with persistence.(7, 8) However, for the majority of risk factors examined to date (e.g. chemotherapy, breast cancer stage) findings have either been mixed or null.(7, 8) Moreover, information on many of these risk factors is not readily available to the treating oncologist, and therefore has limited applicability in clinical practice in terms of helping to identify those women at risk of future non-persistence. A more thorough understanding of the contribution of demographic, clinical and treatment-related risk factors, which are readily available to the treating oncologist, to hormonal therapy MTB may help identify subgroups of women at higher risk of non-adherence or non-persistence at

treatment initiation. These women may benefit from an early intervention or additional support to persist with treatment. Knowledge of these risk factors at treatment initiation may also be used to develop a risk prediction tool for oncologists, which would have the potential to support clinical-decision making and could be used to estimate and communicate the risk of hormonal therapy non-persistence to women with breast cancer.(9)

Developing interventions that can optimise hormonal therapy MTB in women with breast cancer is an important challenge. Any such interventions are likely to be resource intensive and costly and therefore need to be targeted at women at higher risk of non-adherence or non-persistence. The aim of this study was to investigate whether demographic, clinical and treatment-related risk factors, available at treatment initiation can be used to reliably predict hormonal therapy non-persistence in women with stage I-III breast cancer to help inform the development of targeted interventions.

Methods

Setting & Data Source

The study was conducted using individual-level patient records from the National Cancer Registry Ireland (NCRI), which have been linked to pharmacy claims data from Ireland's Primary Care Reimbursement Services (PCRS). These linked data have been described previously.(3) The NCRI database records detailed demographic and clinical information for all incident cancers diagnosed in the population usually resident in Ireland. Completeness of registration is high, especially for breast cancer.(10) The PCRS database records details of claims from pharmacies for financial reimbursement of medications dispensed to approximately one third (1.4 million) of the Irish population who have eligibility for the General Medical Services (GMS) scheme. Eligibility for the scheme (which provides free access to public health services and heavily subsidised prescribed medications) is assessed by a combination of means-test and age. The use for research of de-identified data held by the NCRI is covered by the Health (Provision of Information) Act 1997.

Cohort Definition

Our study cohort was defined as all women with a diagnosis of stage I-III, oestrogen (ER) or progesterone (PR) receptor positive breast cancer diagnosed 2001-2008, who had received tumour directed surgery and had subsequently filled at least one prescription for hormonal therapy (selective estrogen receptor modulator, SERM; aromatase inhibitor, AI) within one year of breast cancer diagnosis. Women also had to have GMS eligibility from one year prior to hormonal therapy initiation to at least the end of follow-up which was defined as the first of treatment discontinuation, disease recurrence, death or 5 years of completed hormonal therapy treatment. Women were excluded if they had previously been diagnosed with another invasive cancer other than non-melanoma skin cancer. Deaths (from all causes) were identified from

linked death certificates. Recurrences were identified from medical records by NCRI tumour registration officers and pathology reports of biopsied breast tumour metastases reported to the NCRI. Two separate cohorts of women were identified; women with a 5 year follow-up period and women with a 1 year follow-up period.

Hormonal therapy MTB

The date of dispensing, drug name and number of days' supply on each prescription for hormonal therapy was identified from the PCRS database using WHO-ATC classifications for SERM and AI (Supplementary Table 1). This data was used to assemble a longitudinal daily history of hormonal therapy availability for each woman by assigning the days' supply from each prescription to sequential days from the date of dispensing.(3, 11) These longitudinal histories were used to identify women who discontinued hormonal therapy within 5 years of initiating treatment. Treatment discontinuation (non-persistence) was defined as a gap in treatment of at least 180 days. We also calculated hormonal therapy adherence while on treatment as the proportion of days with a supply of hormonal therapy available up to the first of either treatment discontinuation or the end of follow-up (1 year or 5 years after initiation).(3)

Risk factors for hormonal therapy MTB

We previously conducted a systematic literature review to identify all risk factors that have been statistically significantly associated with hormonal therapy adherence or persistence.(8) (Supplementary Table 2) From these we selected demographic, clinical and treatment-related "baseline risk factors" i.e. factors which could, or would (in most settings), be assessed prior to, or at the time of, hormonal therapy initiation and are therefore likely to be routinely available to a prescriber/treating oncologist (Supplementary Table 2); for example, data collected during a "normal" medical history taking and examination.

Based on the baseline risk factors identified in our systematic review (Supplementary Table 2), we extracted the following demographic, clinical and treatment-related variables from the NCRI-PCRS database: age at diagnosis (categorised as <50, 50-65, >65 for analysis); marital status; occupation; residential location(12); socioeconomic status, from a census-based deprivation score (5 levels ranging from least to most deprived)(13); smoking status; number of regular medications used prior to diagnosis (0, 1-4, ≥5); hormone replacement therapy (HRT) use prior to diagnosis; antidepressant use prior to hormonal therapy initiation; ER/PR status (ER+PR+, ER+PR-, ER-PR+); HER2 status (positive, negative, unspecified); tumor grade (low, intermediate, high, unspecified); lymph node status (positive, negative, unspecified); tumor size (<2cm, 2-5cm, >5cm, unspecified); receipt of surgery/radiation (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation); receipt of chemotherapy; and type of hormonal therapy prescribed (SERM, AI). A small number (n=3) of baseline risk factors identified in our systematic review (Supplementary Table 2) were either not available in the NCRI-PCRS database or not applicable to our study cohort.

Statistical Analysis

Kaplan Meier plots were used to estimate the cumulative probability of hormonal therapy non-persistence in the first five years of treatment with censoring at breast cancer recurrence or death. The distribution of demographic, clinical and treatment-related baseline risk factors was compared between women who completed five years of adjuvant hormonal therapy and women who did not using relative risks (RR) and risk differences (RD). Multivariate binomial models were used to estimate adjusted RR and RD (logit and identity link used respectively) with 95% confidence intervals (CI) for associations between all baseline risk factors and hormonal therapy non-persistence.(14, 15) The baseline risk factors were initially fitted individually then fitted simultaneously.

The performance of this model (Model 1: 5 year cohort) for predicting hormonal therapy non-persistence prior to completing at least five years of treatment was evaluated. Firstly calibration was assessed by stratifying patients into predicted non-persistence risk deciles and plotting the observed proportions of non-persistence within each decile. Secondly the discriminative performance the model was assessed by the area under the receiver-operating characteristic (ROC) curve (AUC).(16)

The possibility that demographic, clinical and treatment-related baseline risk factors would have a stronger influence on early treatment non-persistence was also considered and analyses were repeated for treatment non-persistence occurring only in the first year following treatment initiation (Model 2: 1 year cohort). Non-persistence was measured as a gap in treatment of ≥180 days. Studies have indicated that the incidence and determinants of hormonal therapy non-persistence may vary between early and later years of treatment.(6, 17, 18)

All analyses were conducted using SAS® v9.3 (SAS® Institute Inc, Cary, NC) and results were considered statistically significant at a two-sided α-level of 0.05.

Results

Cohort characteristics

We identified 3,415 women from the linked NCRI-PCRS database with a diagnosis of stage I-III oestrogen (ER) or progesterone (PR) receptor positive breast cancer, who received tumour directed surgery followed by hormonal therapy with either a SERM or AI with a 5 year follow-up period. The median time from diagnosis to hormonal therapy initiation was 172 days (IQR; 66, 223). The characteristics of these women are presented in Table 1. The mean age of women was 61.4 years (SD=12.6), and 52.3% of women were prescribed tamoxifen as their first hormonal therapy (Anastrazole 37.6%, Letrozole 9.8%, Exemestane 0.3%). We identified 6,609 women from the linked NCRI-PCRS database with a 1 year follow-up period. The characteristics of these women are similar and presented in Table 2.

Hormonal therapy MTB

Within the 5 year follow-up cohort, we identified 680 women (19.9%) who stopped refilling prescriptions for their hormonal therapy prior to a breast cancer recurrence, death or completing at least five years of treatment. Women were followed for a total of 12,436 person years and the hormonal therapy discontinuation rate was 54.7 per 1000 woman years of hormonal therapy treatment. The cumulative probability of non-persistence at one, three, and five years after hormonal therapy initiation was 7.6% (95%CI 8.4%, 6.7%), 14.5% (95%CI 15.8%, 13.3%) and 21.6% (95%CI 23.1%, 20.2%) respectively. In addition, we identified 390 (11.4%) women in our study population who were <80% adherent with treatment during the time that they were taking it. Overall, due to either non-persistence or non-adherence, 761 (22.3%) women received <80% of the doses required to complete five years of adjuvant hormonal therapy.

Within the 1 year follow-up cohort, 412 women (6.2%) stopped refilling prescriptions for their hormonal therapy prior to a breast cancer recurrence, death or completing at least one year of treatment and 742 (11.2%) were <80% adherent with treatment. In total, 997 (15.1%) women were either non-persistent or non-adherent within the first year of adjuvant hormonal therapy treatment.

Validation & predictive ability of baseline risk factors for non-persistence

Model 1: non-persistence within 5 years

In multivariable Model 1, which included all of the previously identified demographic, clinical or treatment-related baseline risk factors, four baseline characteristics were statistically significantly associated with not completing 5 years of hormonal therapy (Table 1). Compared to women aged 50-65 years, women aged <50 years (adjusted RR 1.41 95% CI 1.16, 1.70), and women prescribed antidepressants (RR 1.22 95% CI 1.04, 1.45), were at significantly increased risk of non-persistence. Women who were married (RR 0.82 95% CI 0.71, 0.94) and women who had a history of medication use prior to their breast cancer diagnosis (>5 medications vs none: RR 0.61 95% CI 0.50, 0.75) had a significantly reduced risk of non-persistence. We found marginal, non-significant, associations with non-persistence for several other risk factors, including the type of surgery/radiation received (Table 1). Individually the risk factors were associated with up to a 7% increase (age <50 years) or 9% decrease (prior history of medication use) in the absolute risk of non-persistence (Table 1).

The ROC curve for Model 1 is presented in Figure 1. The Hosmer-Lemeshow goodness of fit test was p=0.88. The AUC for this ROC curve was 0.61 which suggests not particularly good prediction of non-persistence with these baseline risk factors at 5 years.

Model 2: early non-persistence

In Model 2, of all of the previously identified demographic, clinical or treatment-related baseline risk factors, three characteristics were statistically significantly associated with not completing 1 year of hormonal therapy (Table 2). Compared to women aged 50-65 years, women aged >65 years were at significantly increased risk of non-persistence (adjusted RR 1.45 95% CI 1.11, 1.86). Similar to Model 1, women who were married (RR 0.79 95% CI 0.64, 0.96) and women who had a history of medication use prior to their breast cancer diagnosis (>5 medications vs. none: RR 0.36 95% CI 0.27, 0.48) had a significantly reduced risk of non-persistence (Table 2). The ROC curve for Model 2 is presented in Figure 2. The results were similar to Model 1 and the AUC for the ROC curve was 0.63 (Figure 2). The Hosmer-Lemeshow goodness of fit test was p=0.86.

Discussion

Summary of findings

The aim of this study was to investigate whether demographic, clinical and treatment-related information likely to be routinely available at hormonal therapy initiation could be used to reliably predict non-persistence in women with stage I-III breast cancer. The development of such a risk prediction model would enable clinicians to identify at baseline women likely to be non-persistent, to whom targeted support could be provided thereby maximising persistence and maximising clinical outcomes. However, only four of 17 previously identified risk factors (age, marital status, previous medication use and antidepressant use) were statistically significantly associated with completing five years of hormonal therapy. Moreover, our risk prediction model containing all risk factors did not discriminate well between women at high risk of hormonal therapy non-persistence at treatment initiation from those at lower risk. The same conclusion held when early non-persistence was considered (within 1 year of initiation).

The rate of adjuvant hormonal therapy non-persistence in the current study (19.9%) at 5 years is somewhat lower than discontinuation rates of 31-73% and 47.1% by five years reported in previous studies.(7, 19) The definition of non-persistence in the current study was based on a gap of at least 6 months in filling prescriptions for hormonal therapy while previous studies have measured non-persistence using shorter refill gaps of 45-90 days in treatment.(20-22) Our rate of non-persistence was also adjusted for women who had stopped their hormonal therapy due to a breast cancer recurrence, which previous studies have not always done.

In the current study, younger women (aged <50 years) had an increased risk of discontinuing hormonal therapy within 5 years, while older women (aged >65 years) had an increased risk of discontinuing hormonal therapy within 1 year. Extremes of age (e.g. older and younger women)

have been shown to be largely negatively associated with hormonal therapy persistence and middle aged women (50-65 years) may be the most persistent.(7, 17, 23) Younger women have reported more difficulties in coping with breast cancer and more concerns over loss of fertility and femininity associated with hormonal therapy.(24) These concerns may also become less acceptable to younger women over time. Hormonal therapy side-effects have also been found to be associated with non-persistence in younger women during the later years of treatment (> 16 months).(18) Early non-persistence in older women may be influenced by psychosocial factors such as lack of social support and a higher incidence of cognitive and functional impairment.(25) There is some evidence of hormonal therapy having a negative influence on cognition within the first year of treatment and this may be more evident in older populations.(26)

Women taking more medications at baseline had a reduced risk of hormonal therapy non-persistence, findings similar to those of previous studies.(6, 17, 20, 27) Studies have also shown that patients who are medication naïve have a higher risk of non-persistence and the provision of aids (e.g. pill boxes) and action planning techniques (e.g. prompts or cues to take hormonal therapy) at treatment initiation may improve MTB.(28) Findings in previous studies were mixed for associations between marital status and antidepressant use and hormonal therapy persistence.(17, 18, 20) In the current study, married women had a reduced risk of hormonal therapy non-persistence within 1 and 5 years, while women prescribed antidepressants had an increased risk of non-persistence within 5 years. Marital status and social support have been reported to increase adherence to medical regimens in general, while depression is associated with reduced adherence.(29, 30) Spousal assistance may be associated with increased persistence through providing practical support (e.g. reminding patient to take hormonal therapy) while depression is often associated with social isolation and withdrawal from those who provide emotional support and assistance.(30, 31)

The risk factors identified in our systematic review and examined in our models provided limited evidence on identifying a subgroup of women towards whom strategies to in which to promote adherence or persistence with hormonal therapy might be targeted. There was some evidence that subgroups of younger and older women and those with no prior history of medication use may benefit from an intervention to support hormonal therapy MTB. Hence, despite a relatively large evidence base identifying and measuring demographic, clinical and treatment-related risk factors for hormonal therapy non-persistence our study suggests that these risk factors have limited predictive ability in identifying women at future risk of hormonal therapy non-persistence and are, therefore, of only minimal clinical utility in practice.(7, 8) In order to better predict women at high risk of non-persistence, it is likely that these demographic, clinical and treatment-related risk factors need to be combined with additional behavioural and psychological risk factors. For example, lower perceived necessity of treatment and a lack of belief in the efficacy of hormonal therapy have been shown to be associated with hormonal therapy non-persistence (32-34) and good physician-patient communication and collaborative decision-making has been found to be highly positively correlated with treatment adherence.(35) An assessment of these types of factors could potentially be undertaken at treatment initiation; such an assessment for non-persistence could include measuring patients beliefs about their hormonal therapy (e.g. risks, benefits, treatment efficacy) as well as assessing potential difficulties of remaining adherent with long-term therapy at treatment initiation.(36) Evaluation of the discriminative performance of models containing these types of factors, as well as demographic, clinical and treatment-related factors, is warranted.

A consistent finding in the literature is that experience of side-effects is associated with hormonal therapy non-persistence.(8, 37-40) However, their impact on breast cancer patients' quality of life is often underestimated by clinicians.(41) Motivation to persist with hormonal therapy may be influenced by women's acceptability of treatment side-effects and quality of life

preferences.(42) There is some evidence that switching hormonal therapy and developing patient self-management skills may potentially ease the side-effects burden and increase persistence with treatment.(43) A variety of treatments, including progestins, androgens, SSRIs and acupuncture have also shown efficacy in reducing hot flashes.(44, 45) Side-effects usually develop within the first few months of treatment initiation and could be evaluated and managed during initial clinic visits.(39) This information, alongside an assessment of women's coping mechanisms could also be included in a baseline predictive model of non-persistence.

Strengths and limitations

This population-based cohort study, based on high quality prospectively collected prescription and cancer registry data, is the first to assess the discriminative performance of a large number of risk factors likely to be routinely available at baseline to the treating oncologist in predicting women at future risk of non-persistence. It is also one of only a small number of studies which have examined the impact of demographic, clinical and treatment-related risk factors on initial hormonal therapy persistence and persistence over 5 years – the minimum time frame of use recommended to achieve therapeutic benefit.(17, 21, 46) There are, however, limitations to this study. We were unable to determine the reasons for treatment non-adherence and non-persistence and information was not available on a few demographic, clinical and treatment-related variables which have previously been associated with non-persistence (e.g. presence of diabetes).(47) The cohort was based on a subset of women with medical card eligibility and may not represent MTB in women who pay for their prescriptions. However previous studies have found no association between monthly cost of hormonal therapy and non-persistence.(33, 37) The assessment of MTB was based upon prescription refill data and may therefore overestimate true adherence and persistence; however, use of prescription claims databases to estimate MTB has been validated in other studies.(48)

Implications & conclusions

To date only a minority of published medication adherence enhancing interventions have demonstrated improved MTB or enhanced patient outcomes. These interventions were generally complex incorporating several different approaches and involving a range of health professionals.(49) Our findings indicate that demographic, clinical and treatment-related risk factors alone have limited predictive ability in identifying women at risk of hormonal therapy non-persistence. Persistence and adherence to hormonal therapy is influenced by a number of factors; some of these related to the patient and their medical history (e.g. patient's age, history of prior medication use) but others do not (e.g. beliefs about the risks and benefits of treatment, experience of adverse effects and a good patient-physician relationship). A combination of a baseline demographic and clinical and treatment-related risk-factor assessment, a baseline psychological (beliefs/perceptions of treatment) assessment and an early post initiation follow-up assessment of side effects may be better at identifying those women at highest risk of hormonal therapy non-persistence and possibly at greatest likelihood of benefiting from intervention. Further studies of this integrated approach would be more informative than studies investigating and identifying individual risk factors. Such studies may ultimately improve hormonal therapy persistence and reduce breast cancer recurrence and mortality among women with breast cancer.

Conflict of interest

The authors declare that they have no conflict of interest

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Table 1: Multivariate relative risks (RR) and risk differences (RD) for the association between baseline risk factors and hormonal therapy non-persistence within 5 years of initiating treatment (N=3,415)

Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 1: Adjusted RR (95% CI)	Model 1: Adjusted RD (95% CI)
Age at diagnosis	<50	697 (20.4)	517 (74.2)	180 (25.8)	**1.41 (1.16, 1.70)**	**0.07 (0.03, 0.11)**
	50-65	1309 (38.3)	1074 (82.1)	235 (17.9)	Ref	Ref
	> 65	1409 (41.2)	1144 (81.2)	265 (18.8)	1.07 (0.89, 1.29)	0.02 (-0.02, 0.05)
Marital status	Other	1536 (44.9)	1207 (78.6)	329 (21.4)	Ref	Ref
	Married	1879 (55.1)	1528 (81.3)	351 (18.7)	**0.82 (0.70, 0.94)**	**-0.04 (-0.07, -0.01)**
Occupational status	Other	2715 (79.5)	2159 (79.5)	556 (20.5)	Ref	Ref
	Homemaker	700 (20.5)	576 (82.3)	124 (17.7)	0.94 (0.78, 1.12)	-0.01 (-0.05, 0.02)
Residential location	Urban	2102 (61.5)	1691 (80.5)	411 (19.5)	Ref	Ref
	Rural	1313 (38.5)	1044 (79.5)	269 (20.5)	1.03 (0.88, 1.20)	0.01 (-0.02, 0.04)
Smoking status	Never	1724 (50.5)	1375 (79.8)	349 (20.2)	Ref	Ref
	Current	789 (23.1)	639 (81.0)	150 (19.0)	0.91 (0.76, 1.09)	-0.02 (-0.05, 0.01)
	Former	417 (12.2)	332 (79.6)	85 (20.4)	1.03 (0.84, 1.27)	0.00 (-0.05, 0.04)
	Unspecified	485 (14.2)	389 (80.2)	96 (19.8)	0.95 (0.78, 1.17)	-0.01 (-0.05, 0.03)
Deprivation category	1 (Least Deprived)	443 (12.9)	358 (80.8)	85 (19.2)	Ref	Ref
	2	404 (11.8)	319 (79.0)	85 (21.0)	1.10 (0.84, 1.44)	0.02 (-0.03, 0.07)
	3	452 (13.2)	365 (78.8)	96 (21.2)	1.10 (0.85, 1.42)	0.02 (-0.03, 0.07)
	4	626 (18.3)	497 (79.4)	129 (20.6)	1.07 (0.84, 1.38)	0.02 (-0.03, 0.07)
	5 (Most Deprived)	1280(37.5)	1037 (81.0)	243 (19.0)	1.03 (0.82, 1.29)	0.01 (-0.04, 0.05)
	Unspecified	210 (6.2)	168 (80.0)	42 (20.0)	1.06 (0.75, 1.49)	0.03 (-0.04, 0.09)
Number of regular meds used pre-diagnosis	0	1212 (35.5)	913 (75.3)	299 (24.7)	Ref	Ref
	1 - 4	842 (24.7)	685 (81.4)	157 (18.6)	**0.73 (0.60, 0.88)**	**-0.06 (-0.11, -0.03)**

Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 1: Adjusted RR (95% CI)	Model 1: Adjusted RD (95% CI)
	≥ 5	1361 (39.8)	1137 (83.5)	224 (16.5)	**0.61 (0.50, 0.75)**	**-0.09 (-0.13, -0.06)**
HRT use	No	2914 (85.3)	2312 (79.3)	602 (20.7)	Ref	Ref
	Yes	501 (14.7)	423 (84.4)	78 (15.6)	0.90 (0.72, 1.14)	-0.01 (-0.05, 0.02)
Antidepressant use	No	2713 (79.4)	2182 (80.4)	531 (19.6)	Ref	Ref
	Yes	702 (20.6)	553 (78.8)	149 (21.2)	**1.22 (1.04, 1.45)**	**0.04 (0.01, 0.08)**
ER/PR Status*	ER+/PR+	2250 (65.9)	1799 (80.0)	451 (20.0)	Ref	Ref
	ER+/PR-	1058 (31.0)	850 (80.3)	208 (19.7)	1.01 (0.87, 1.18)	0.01 (-0.02, 0.04)
	ER-/PR+	107 (3.1)	86 (80.4)	21 (19.6)	0.92 (0.63, 1.37)	-0.01 (-0.09, 0.07)
HER2 Status	Negative	2140 (62.7)	1732 (80.9)	408 (19.1)	Ref	Ref
	Positive	391 (11.5)	309 (79.0)	82 (21.0)	1.04 (0.84, 1.28)	0.02 (-0.02, 0.07)
	Unspecified	884 (25.9)	694 (78.5)	190 (21.5)	1.13 (0.96, 1.32)	0.03 (0.00, 0.06)
Tumour Size	< 2 cm	1438 (42.1)	1133 (78.8)	305 (21.2)	Ref	Ref
	2-5 cm	1574 (46.1)	1276 (81.1)	298 (18.9)	0.92 (0.79, 1.07)	-0.02 (-0.05, 0.01)
	> 5 cm	385 (11.3)	314 (81.6)	71 (18.4)	0.89 (0.70, 1.15)	-0.03 (-0.07, 0.02)
	Unspecified	18 (0.53)	12 (66.7)	6 (33.3)	1.26 (0.64, 2.47)	0.07 (-0.15, 0.29)
Nodal Status	Negative	1651 (48.4)	1325 (80.3)	326 (19.8)	Ref	Ref
	Positive	1639 (47.9)	1318 (80.4)	321 (19.6)	1.00 (0.86, 1.17	0.00 (-0.03, 0.03)
	Unspecified	125 (3.7)	92 (73.6)	33 (26.4)	1.19 (0.85, 1.66)	0.05 (-0.03, 0.13)
Tumour Grade	Low	350 (10.2)	280 (80.0)	70 (20.0)	Ref	Ref
	Intermediate	1805 (52.9)	1455 (80.6)	350 (19.4)	1.03 (0.82, 1.29)	0.01 (-0.04, 0.05)
	High	986 (28.9)	788 (79.9)	198 (20.1)	1.05 (0.82, 1.35)	0.01 (-0.04, 0.06)
	Unspecified	274 (8.0)	212 (77.4)	62 (22.6)	1.11 (0.82, 1.51)	0.03 (-0.03, 0.10)
Surgery / Radiation	Mastectomy	1793 (52.5)	1463 (81.6)	330 (18.4)	Ref	Ref
	Breast conserving surgery + radiation	1465 (42.9)	1154 (78.8)	311 (21.2)	1.16 (1.00, 1.34)	0.03 (0.00, 0.06)

Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 1: Adjusted RR (95% CI)	Model 1: Adjusted RD (95% CI)
	Breast conserving surgery - radiation	157 (4.6)	118 (75.2)	39 (24.8)	1.36 (0.99, 1.86)	0.06 (-0.01, 0.13)
Chemotherapy	No	1659 (48.6)	1335 (80.5)	324 (19.5)	Ref	Ref
	Yes	1756 (51.4)	1400 (79.7)	356 (20.3)	0.88 (0.74, 1.06)	-0.02 (-0.05, 0.02)
Hormonal Therapy	AI	1627 (47.6)	1309 (80.5)	318 (19.5)	Ref	Ref
	SERM	1788 (52.4)	1426 (79.8)	362 (20.2)	0.90 (0.78, 1.04)	-0.01 (-0.04, 0.02)

Women with stage I-III oestrogen (ER) or progesterone (PR) receptor positive breast cancer diagnosed 2001-2008, received tumour directed surgery and filled at least one prescription for hormonal therapy (selective estrogen receptor modulator, SERM; aromatase inhibitor, AI) within one year of breast cancer diagnosis and with 5 years of follow-up data.

HRT= hormone replacement therapy, ER/PR status= estrogen receptor/progesterone receptor status, HER2 status= human epidermal growth factor receptor 2

Relative risks (RR) and relative differences (RD) are mutually adjusted for all demographic, clinical or treatment-related baseline risk factors shown in the table. No significant collinearity was found between the risk factors.

Table 2: Multivariate relative risks (RR) for the association between baseline risk factors and hormonal therapy non-persistence within 1 year of initiating treatment (N=6,609)

Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 2: Adjusted RR (95% CI)	Model 2: Adjusted RD (95% CI)
Age at diagnosis	<50	1,539 (23.3)	1,437 (93.4)	102 (6.6)	1.07 (0.82, 1.40)	0.01 (-0.02, 0.02)
	50-65	2,709 (41.0)	2,557 (94.4)	152 (5.6)	Ref	Ref
	> 65	2,361 (35.7)	2,203 (93.3)	158 (6.7)	**1.44 (1.11, 1.86)**	**0.02 (0.01, 0.04)**
Marital status	Other	2,786 (42.2)	2,590 (93.0)	196 (7.0)	Ref	Ref
	Married	3,823 (57.8)	3,607 (94.4)	216 (5.6)	**0.79 (0.64, 0.96)**	**-0.01 (-0.03, 0.00)**
Occupational status	Other	5,166 (78.2)	4,841 (93.7)	325 (6.3)	Ref	Ref
	Homemaker	1,433 (21.8)	1,356 (94.0)	87 (6.0)	1.08 (0.85, 1.36)	0.00 (-0.02, 0.02)
Residential location	Urban	4,087 (61.8)	3,842 (94.0)	245 (6.0)	Ref	Ref
	Rural	2,522 (38.2)	2,355 (93.4)	167 (6.6)	1.16 (0.93, 1.42)	0.01 (-0.01, 0.03)
Smoking status	Never	3,213 (48.6)	3,021 (94.0)	192 (6.0)	Ref	Ref
	Current	1,436 (21.7)	1,341 (93.4)	95 (6.6)	1.15 (0.90, 1.47)	0.01 (-0.01,0.03)
	Former	795 (12.0)	741 (93.2)	54 (6.8)	1.14 (0.85, 1.52)	0.01 (-0.02, 0.03)
	Unspecified	1,165 (17.6)	1,094 (93.9)	71 (6.1)	1.00 (0.76, 1.31)	0.00 (-0.02, 0.02)
Deprivation category	1 (Least Deprived)	880 (13.3)	832 (94.6)	48 (5.4)	Ref	Ref
	2	821 (12.4)	767 (93.4)	54 (6.6)	1.24 (0.85, 1.79)	0.01 (-0.02, 0.04)
	3	861 (13.0)	802 (93.2)	59 (6.8)	1.31 (0.90, 1.88)	0.02 (-0.01, 0.05)
	4	1,187 (18.0)	1,114 (93.9)	73 (6.1)	1.17 (0.82, 1.65)	0.01 (-0.02, 0.04)
	5 (Most Deprived)	2,427 (36.7)	2,269 (93.5)	158 (6.5)	1.34 (0.97, 1.83)	0.02 (-0.01,0.04)
	Unspecified	433 (6.6)	413 (93.4)	20 (4.6)	0.99 (0.58, 1.67)	0.00 (-0.03, 0.04)
Number of regular meds used pre-diagnosis	0	2,625 (39.7)	2,418 (92.1)	207 (7.9)	Ref	Ref
	1 - 4	1,444 (21.9)	1,353 (93.7)	91 (6.3)	**0.59 (0.44, 0.77)**	**-0.03 (-0.05, -0.01)**

Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 2: Adjusted RR (95% CI)	Model 2: Adjusted RD (95% CI)
	≥ 5	2,540 (38.4)	2,426 (95.5)	114 (4.5)	**0.35 (0.26, 0.48)**	**-0.5 (-0.07, -0.03)**
HRT use	No	5,683 (86.0)	5,325 (93.7)	358 (6.3)	Ref	Ref
	Yes	926 (14.0)	872 (94.2)	54 (5.8)	1.25 (0.93, 1.68)	0.01 (-0.01, 0.03)
Antidepressant use	No	5,247 (79.4)	4,920 (93.8)	327 (6.2)	Ref	Ref
	Yes	1,326 (20.6)	1,277 (93.8)	85 (6.2)	1.21 (0.95, 1.54)	0.01 (-0.01, 0.03)
ER/PR Status*	ER+/PR+	4,550 (68.9)	4,278 (94.0)	272 (6.0)	Ref	Ref
	ER+/PR-	1,911 (28.9)	1,782 (93.2)	129 (6.8)	1.13 (0.91, 1.39)	0.01 (-0.01, 0.03)
	ER-/PR+	148 (2.2)	137 (92.6)	11 (7.4)	1.15 (0.63, 2.03)	0.01 (-0.05, 0.06)
HER2 Status	Negative	4,791 (72.5)	4,514 (94.2)	277 (5.8)	Ref	Ref
	Positive	799 (12.1)	750 (93.9)	49 (6.1)	1.01 (0.74, 1.36)	-0.00 (-0.03, 0.02)
	Unspecified	1,019 (15.4)	933 (91.6)	86 (8.4)	1.28 (1.01, 1.61)	0.02 (-0.01, 0.04)
Tumour Size	< 2 cm	2,845 (43.0)	2,665 (93.7)	180 (6.3)	Ref	Ref
	2-5 cm	3,032 (45.9)	2,850 (94.0)	182 (6.0)	0.94 (0.76, 1.17)	-0.01 (-0.02, 0.01)
	> 5 cm	688 (10.4)	642 (93.3)	46 (6.7)	0.99 (0.70, 1.38)	-0.00 (-0.03, 0.03)
	Unspecified	44 (0.7)	40 (90.9)	4 (9.1)	1.07 (0.34, 2.64)	0.00 (-0.11, 0.11)
Nodal Status	Negative	3,196 (48.4)	3,010 (94.2)	186 (5.8)	Ref	Ref
	Positive	3,207 (48.5)	3,003 (93.6)	204 (6.4)	1.11 (0.89, 1.37)	0.01 (-0.01, 0.02)
	Unspecified	206 (3.1)	184 (89.3)	22 (10.7)	1.48 (0.96, 2.22)	0.04 (-0.01, 0.09)
Tumour Grade	Low	691 (10.5)	649 (93.9)	42 (6.1)	Ref	Ref
	Intermediate	3,693 (55.9)	3,467 (93.9)	226 (6.1)	1.04 (0.75, 1.44)	-0.00 (-0.03, 0.03)
	High	1,863 (28.1)	1,759 (94.4)	104 (5.6)	0.93 (0.64, 1.34)	-0.00 (-0.03, 0.02)
	Unspecified	362 (5.5)	322 (88.9)	40 (11.1)	1.62 (1.09, 2.33)	0.04 (-0.01, 0.08)
Surgery / Radiation	Mastectomy	3,106 (47.0)	2,907 (93.6)	199 (6.4)	Ref	Ref
	Breast conserving surgery + radiation	3,239 (49.0)	3,052 (94.2)	187 (5.8)	0.95 (0.77, 1.18)	-0.00 (-0.02, 0.020

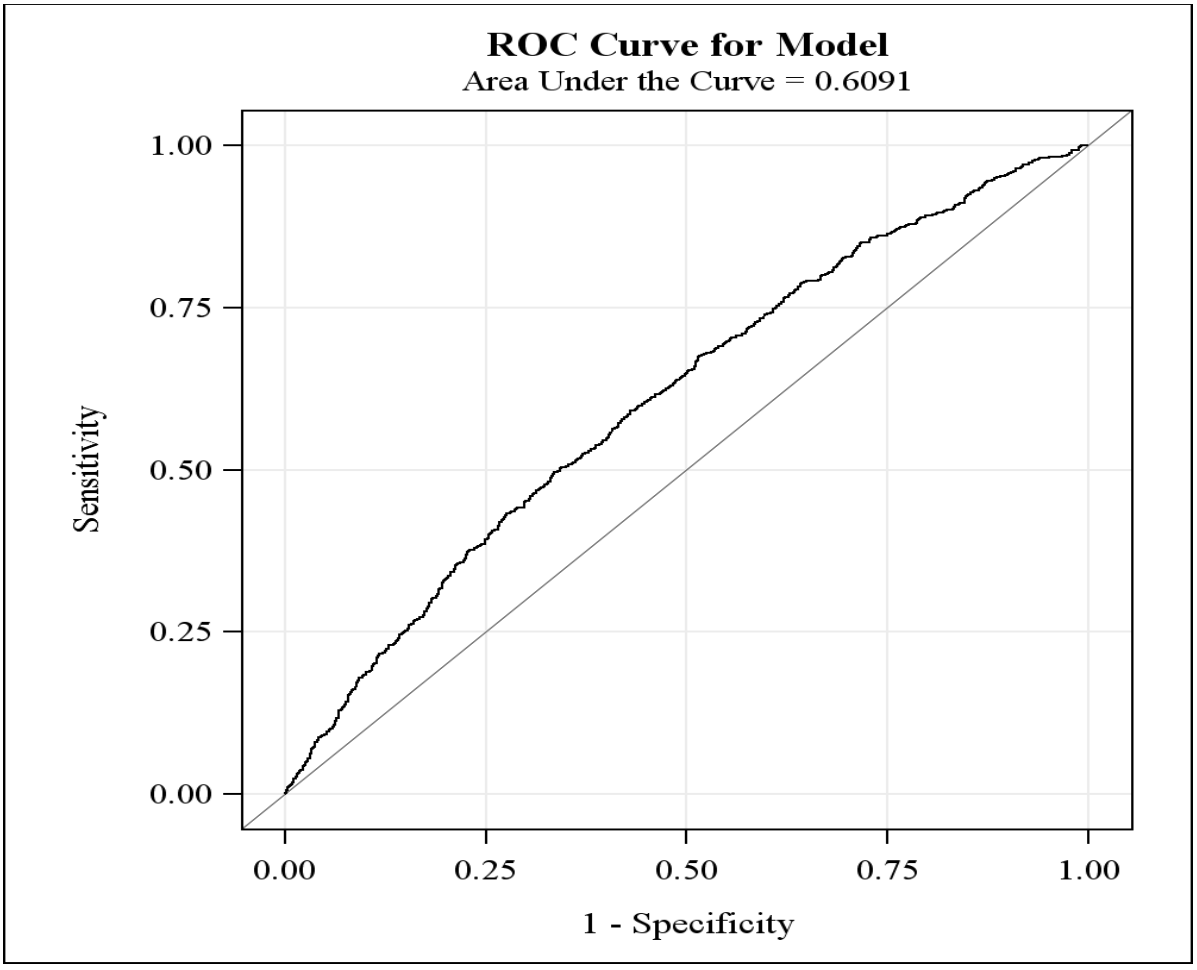
Risk factor		Total N (%)	Persistent N (%)	Non-persistent N (%)	Model 2: Adjusted RR (95% CI)	Model 2: Adjusted RD (95% CI)
	Breast conserving surgery - radiation	264 (4.0)	238 (90.2)	26 (9.8)	1.47 (0.97, 2.14)	0.03 (-0.01, 0.08)
Chemotherapy	No	3,024 (45.8)	2,827 (93.5)	197 (6.5)	Ref	Ref
	Yes	3,585 (54.2)	3,370 (94.0)	215 (6.0)	0.78 (0.60, 1.01)	-0.01 (-0.03, 0.01)
Hormonal Therapy	AI	3,343 (50.6)	3,146 (94.1)	197 (5.9)	Ref	Ref
	SERM	3,266 (49.4)	3,051 (93.4)	215 (6.6)	1.07 (0.86, 1.31)	0.01 (-0.01, 0.03)

Women with stage I-III oestrogen (ER) or progesterone (PR) receptor positive breast cancer diagnosed 2001-2008, received tumour directed surgery and filled at least one prescription for hormonal therapy (selective estrogen receptor modulator, SERM; aromatase inhibitor, AI) within one year of breast cancer diagnosis and with 1 year of follow-up data.

HRT= hormone replacement therapy, ER/PR status= estrogen receptor/progesterone receptor status, HER2 status= human epidermal growth factor receptor 2

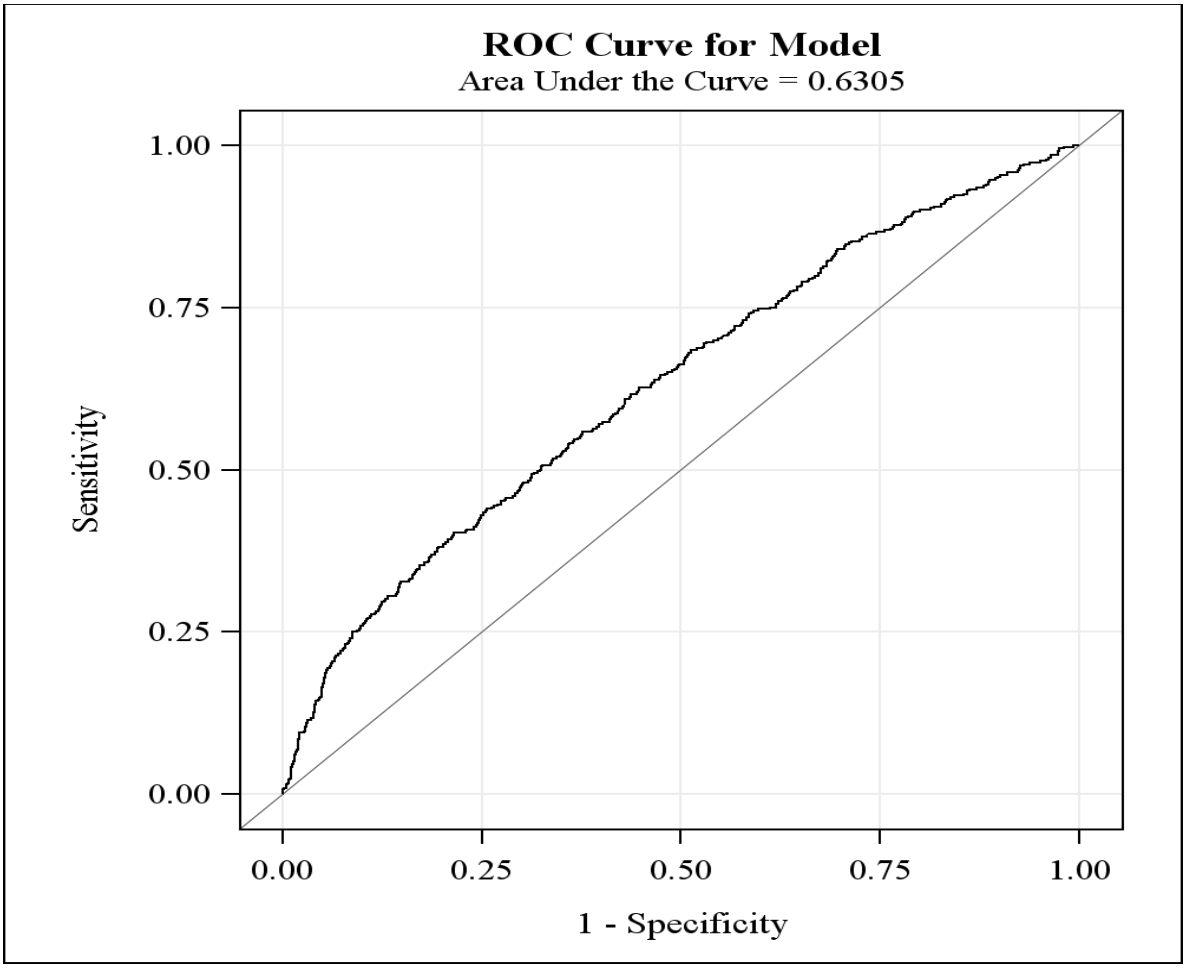
Relative risks (RR) are mutually adjusted for all demographic, clinical or treatment-related baseline risk factors. No significant collinearity was found between the risk factors.

Figure 1: The receiver-operating characteristic (ROC) curve for hormonal therapy non-persistence at 5 years (Model 1)



* including all demographic, clinical or treatment-related baseline risk factors

Figure 2: The receiver-operating characteristic (ROC) curve for hormonal therapy non-persistence at 1 year (Model 2)



* including all demographic, clinical or treatment-related baseline risk factors