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The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study

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Background: Low adherence to adjuvant tamoxifen is associated with worse health outcomes but little is known about the cost-effectiveness of high adherence.

Methods: We conducted an economic evaluation using data for all women with incident breast cancer between 1993 and 2000 who were subsequently prescribed tamoxifen in the Tayside region of Scotland. Patient-level, lifetime Markov models evaluated the impact of high *vs* low adherence to tamoxifen using linked prescribing, cancer registry, clinical cancer audit, hospital discharge and death records. Direct medical costs were estimated for each patient and quality-of-life weights were assigned. Recurrence information was collected by case note review and adherence calculated from prescribing records with low adherence classed below 80%.

Results: A total of 354 (28%) patients had a recorded recurrence and 504 (39%) died. Four hundred and seventy-five (38%) patients had low adherence over the treatment period, which was associated with reduced time to recurrence of 52% ($P<0.001$). Time to other cause mortality was also reduced by 23% ($P=0.055$) but this was not statistically significant. For an average patient over her lifetime, low adherence was associated with a loss of 1.43 (95% CI: 1.15–1.71) discounted life years or 1.12 (95% CI: 0.91–1.34) discounted quality-adjusted life years (QALYs) and increased discounted medical costs of £5970 (95% CI: £4644–£7372). Assuming a willingness to pay threshold of £25 000 per QALY, the expected value of changing a patient from low to high adherence is £33 897 (95% CI: £28 322–£39 652).

Conclusion: Patients with low adherence have shorter time to recurrence, increased medical costs and worse quality of life. Interventions that encourage patients to continue taking their treatment on a daily basis for the recommended 5-year period may be highly cost-effective.

Randomised clinical trials in early breast cancer have shown that tamoxifen reduces recurrence and mortality in women with oestrogen receptor (ER)- or progesterone receptor (PR)-positive cancers and it is recommended for a 5-year period (Scottish Intercollegiate Guideline Network Guidelines, 2005; Early Breast Cancer Trialists' Collaborative Group, 2011). However, there is a growing evidence that the efficacy of tamoxifen in recurrence and mortality reduction is contingent upon patient adherence, that is, 'the extent to which a patient's behaviour… coincides with medical or health advice' (McDonald *et al*, 2002).

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Studies have reported that one-third to a half of women do not complete the recommended 5-year tamoxifen treatment and that this is associated with an increased mortality risk (Barron *et al*, 2007; Ma *et al*, 2008; McCowan *et al*, 2008; Owusu *et al*, 2008; Yood *et al*, 2008; Narod, 2010; van Herk-Sukel *et al*, 2010; Hershman *et al*, 2011; Murphy *et al*, 2012; Hadji *et al*, 2013; Huiart *et al*, 2013; Makubate *et al*, 2013). Other work has shown that 19–28% of women prescribed adjuvant tamoxifen in the community miss at least one out of five daily doses putting adherence below 80%, a level also associated with increased risk of all-cause mortality (Patridge *et al*, 2003; McCowan *et al*, 2008; Dezentje *et al*, 2010; Hershman *et al*, 2010, 2011; Makubate *et al*, 2013).

Economic analyses of adjuvant tamoxifen have shown benefits, an early study using trial data reported users gained 0.4 quality-adjusted life years (QALYs) over controls with an incremental cost per QALY gained of AUS$1365 (Glasziou and Haas, 1994). A more recent study using a community-based observational cohort of women with breast cancer in Korea reported that tamoxifen was cost-effective for patients with stage I or II ER- or PR-positive cancers and for all patients with stage III disease (Yang *et al*, 2010). However, we were unable to identify any previous study that has examined the impact of patient adherence on the cost-effectiveness of tamoxifen therapy for early breast cancer. In another field, improving adherence to statins would enhance cost-effectiveness, with a projected decrease in incremental cost per QALY gained from €35 000 to €26 000 for complete adherence (Greving *et al*, 2011).

It is plausible that along with a negative impact on health outcomes, low adherence to adjuvant tamoxifen may also induce higher health-care costs. Patients with low adherence may receive less clinical benefit with lower quality of life and require more long-term health services because of disease recurrence. An economic evaluation relating to the value of adherence to adjuvant tamoxifen is required to inform clinical and policy decisions on designing and evaluating interventions, which improve adherence.

The aims of this study were to investigate patient adherence to tamoxifen in a geographically defined population of women in Tayside, Scotland; to assess the extent to which low adherence affects recurrence, mortality and medical costs after adjusting for important clinical and demographic factors; and to compare the cost-effectiveness of tamoxifen therapy between patients with high and low adherence.

MATERIALS AND METHODS

Women resident in Tayside, UK, diagnosed and treated for breast cancer between January 1993 and December 2008 were identified using previously described methods (McCowan *et al*, 2008; Makubate *et al*, 2013). Only those women resident in Tayside for the entire period of the study, or until death, were included. Community dispensed prescribing, hospital discharge records, cancer registry, cancer audit and General Registrar's Office death certificates were extracted, record-linked and anonymised for each patient.

Patients were excluded from the study population if there was no known cause of death (7), no record of surgical treatment for cancer (569), had received endocrine therapy for more than 6 months before their diagnosis (104), or were known to be enrolled on endocrine trials (52).

Tamoxifen has been used throughout the study period with aromatase inhibitors (AIs) used as adjuvant endocrine therapy since 2001. The decision on which therapy to use is determined by menopausal status, ER/PR status and risk of recurrence. From dispensed prescribing data, 836 (25%) patients received no adjuvant therapy, 2254 (68%) patients were initially prescribed tamoxifen and 249 (7%) were prescribed an AI. Because of a short median follow-up for patients on AIs and to also remove the possibility of selection bias, only patients on tamoxifen diagnosed by the end of December 2000 who did not switch to AIs were included in the analysis; this reduced the sample to 1301 patients.

A further four patients who recurred or died within 60 days of diagnosis and 34 patients who received their first tamoxifen prescription later than 1 year post diagnosis were also excluded.

Adherence. Each tamoxifen prescription was examined and the number of days covered obtained from the number of dispensed tablets and the prescribed daily dose. When tablets or dose were unavailable for a prescription (1.9% of cases) they were imputed according to tablets or dose from the patient's subsequent prescriptions if available or otherwise previous prescriptions. The expected duration of adjuvant therapy was calculated from the number of days elapsed since diagnosis or the first prescription, if earlier, until either recurrence or death, end of the sample period, or the completion of the standard 5-year therapy. Patients close to recurrence or death may be less likely to adhere, thus patients' adherence for the last 60 days before recurrence/death was not included. The absolute adherence for each patient was calculated as the ratio of the total coverage for all the prescriptions relative to the expected duration. Based on the existing literature, low adherence was defined as less than 80% (Murthy *et al*, 2002; Patridge *et al*, 2003; McCowan *et al*, 2008; Makubate *et al*, 2013). In the current paper, low adherence combined those non-persistent with those persistent but not adherent.

Patient and cancer characteristics. Date of diagnosis and age at the time of diagnosis were recorded from clinical cancer records. Scottish Index of Multiple Deprivation quintiles (ranging from 1 to 5 for most to least deprived) were allocated based on each patient's full postcode and provided a proxy for socioeconomic characteristics (Scottish Government, 2012). A Charlson's Index for co-morbidity was derived from hospital discharge records using standard procedures (Deyo *et al*, 1992; Sundararajan *et al*, 2004). The tumour characteristics on presentation were determined using TNM categories (tumour size, nodal status and metastases), pathological grading and ER status. The patients' disease progress was observed using the information on date of death, cause of death, date of recurrence and type of recurrence (e.g., local recurrence, axillary recurrence and distance recurrence).

Markov model. To value the benefit of high *vs* low adherence to tamoxifen, a simulated patient-level Markov model was developed to predict patients' lifetime disease progress and lifetime costs. Rather than using equal length cycles, the model tracks disease progression of the heterogeneous patient population by sampling the time to next event and costs from patient-specific distributions based on the Tayside sample.

Model structure. The Markov model portrays disease progression from the point of initial diagnosis to death (Figure 1). Patients entering the simulation model were defined with the unique attributes of each patient and their cancer but were assumed to be diagnosed in 2000, and to initiate and continue adjuvant tamoxifen therapy for 5 years or until they recurred or died from other causes. Each patient was modelled assuming both high ($\geqslant$80%) and low adherence ($<$80%).

In the first stage of the model, diagnosed patients were subject to patient-specific risks of recurrence or other-cause mortality based on their characteristics. Those predicted to recur then entered the second stage and were subject to risks of breast cancer mortality and other-cause mortality. Within each stage, the model sampled the time to different events from the patient-specific distributions to determine whether the patient makes transitions between health states. Based on existing literature, patients were assumed to be at risk of breast cancer events at least for 15 years after diagnosis

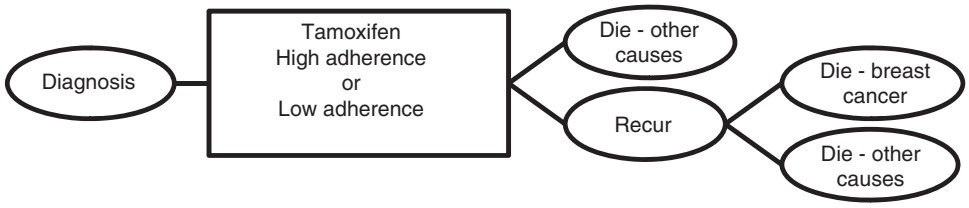

Figure 1. The Markov model for disease progression of breast cancer.

(Delea *et al*, 2007). All patients were also assumed to die from other causes at age 100 years if no event was predicted to occur before then. Direct medical costs were also derived by sampling from patient-specific cost distributions, which were based on their initial characteristics and current health state.

Estimating model parameters

Survival analysis. The simulation of the time to next event involved fitting the sample data to parametric survival-time models and then generating and sampling from the distribution of time to event for each patient. Estimations were conducted for three events separately: diagnosis to recurrence, recurrence to breast cancer mortality and diagnosis to recurrence-free mortality.

In order to predict event time, an accelerated failure time model (AFT model) is adopted, which assumes that the effect of a variate is to multiply the predicted event time by a constant. For each outcome, parametric survival and frailty distributions were fitted and results reported for the model preferred by the AIC selection criteria (Burnham and Anderson, 2004). The parametric survival distributions fitted included exponential, Weibull, Gompertz, lognormal, log-logistic and generalised gamma models, and the frailty distributions included no frailty, gamma and inverse Gaussian models. Because of small numbers, we assumed that other-cause mortality was not influenced by recurrence so the time from recurrence to other-cause death was simulated using the predicted time to recurrence-free mortality (minus time to recurrence).

Whether patients are adherent is based on a number of observable and unobservable characteristics. We included a propensity score within the analysis to allow for possible selection effects based on observed demographic and clinical characteristics (Indurkhya *et al*, 2006). A propensity score was created using a logistic regression model for a patient having low adherence to tamoxifen and fitted in the model as a linear score.

There were 103 patients who had breast cancer as a cause of death but no recorded recurrence information with 77% of these patients diagnosed within the first three sample years (i.e., 1993–1995). To reduce possible bias and account for uncertainty, our analyses used the Multivariate Imputation by Chained Equations method of multiple imputation with five replications of imputed data based on when recurrence occurred between diagnosis and breast cancer death for other patients (Van Buuren *et al*, 1999; Royston, 2004).

QALY. Quality-of-life weights for each health state were drawn from a study of 361 Swedish breast cancer patients in different disease states using preference-based measures (Lidgren *et al*, 2007). The utility value for primary breast cancer (mean: 0.696, 95% CI: 0.634–0.747) was assigned for the first year after diagnosis, after which the mean of utility value increased to 0.779 (95% CI: 0.745–0.811). Once patients recurred, they were assigned the utility for distant recurrence (mean: 0.685, 95% CI: 0.620–0.735) until death. As individual data were not available, we employed the mean and 95% CI to determine the best fitting beta distributions, from which QALYs were sampled for each simulated patient.

Direct medical costs. Direct medical costs for breast cancer and other conditions were estimated using the information on community dispensing and general/acute hospital admissions within the 5-year period after diagnosis. Dispensing was complete over the entire period for specified British National Formulary sections including endocrine therapy, with missing data for some other prescriptions during the periods between April 1997 to March 2000 and January 2002 to December2004.

Unit costs of community dispensing and in-patient hospital admissions were obtained from the Prescription Cost Analysis and 2007/08 Scottish Health Service Costs (ISD Scotland, Scottish Government, 2012a,b). Costs of the most commonly prescribed medication for tamoxifen prescriptions (TAMOXIFEN CIT_TAB 20 MG: £0.07 per quantity) and the average cost among all British National Formulary sections for other prescriptions (£11.67 per dispensed item) were used. In-patient costs were calculated by specialty using costs per case and average length of stay reported for NHS Tayside.

Costs of tamoxifen were estimated for high- and low-adherence patients using the average of adherence within each group, 94.5% and 54.9%, respectively. Patients were assumed to complete 5 years of therapy unless they recurred or died earlier. Costs of other prescriptions and in-patient admissions were estimated for each follow-up year and then modelled using regression methods.

Patient's costs were estimated using a two-part model: (1) a logistic regression for whether patients had any costs; (2) a least squares regression for the log of costs for patient-years with at least some costs. Regressions were based on uncensored patient-years up to 5 years post follow-up. Missing dispensing data were included but controlled for based on the proportion of missing calendar months within each particular follow-up year. In terms of the Markov model, the distribution of costs post 5 years follow-up were assumed to be equivalent to the costs within the 2- to 5-year follow-up period.

Estimating the value of high *vs* low adherence. Outcomes and costs of tamoxifen between high- and low-adherence patients are sampled from the distributions based on the regressions of survival time and medical costs, which are used to estimate lifetime QALYs and costs for each patient. The simulation was programmed using @Risk version 5.7 with 5000 iterations (Palisade. @Risk 5.7. 2009 Ithaca NY: Palisade Corporation). Future costs and benefits were discounted at the annual rate of 3.5%, based on the recommendations of the UK Treasury (National Institute for Health and Clinical Excellence, 2011).

A cost-effectiveness type analysis was conducted to evaluate the economic consequences of a patient choosing high *vs* low adherence to her tamoxifen dispensing, in terms of costs and QALYs gained. The Monte Carlo simulation was used to estimate difference in lifetime cost between high and low adherence (incremental costs) and the difference in lifetime QALYs between the two groups (incremental QALYs). To evaluate the expected value of changing a patient from low adherence to high adherence, we adopted a willingness to pay threshold of £25 000 per QALY (approximately the NICE threshold for recommended adoption of new products) and then the value or net monetary benefit (NMB)

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was calculated as £25 000 per QALY times the difference in QALYs minus the differences in cost (Appleby *et al*, 2007). When generating the patient disease pathways and costs, a probability sensitivity analysis was included where the uncertainty in model parameters estimated and QALYs were also taken into account such that the confidence intervals generated reflect this uncertainty.

Sensitivity analysis. In addition to the probability sensitivity analysis, the robustness of the baseline results was also assessed by a sensitivity analysis where assumptions on both costs and health effects were adjusted. The baseline case allowed annual costs of in-patients and other dispensing to differ because of high or low adherence. In fact, patients with low adherence in our sample were estimated to have a lower probability of incurring costs but once they did incur costs, the cost estimates were significantly higher. In the sensitivity analysis, we considered that these estimates may be a correlated behavioural response, aversion to seeking medical care, rather than the actual impact of low adherence, and examined a scenario where low adherence did not influence costs other than through recurrence or early death. Following NICE guidelines, the impact of varying the duration of the outcomes was also examined by reducing the discount rate for health outcomes from 3.5 to 1.5%.

In addition, our data suggested adherence to medications, in general, diminishes the longer a patient is from initiating medication, thus those who do not recur or die may have lower average adherence levels than those who recurred or died early. Thus, a relative adherence index was also created using the average cumulative adherence index for all patients who had been observed at the same follow-up year for a robustness check. Only the results for absolute adherence are reported given relative adherence produced similar results.

RESULTS

A total of 1263 women prescribed adjuvant tamoxifen survived more than 60 days after diagnosis. There were a total of 525 (42%) deaths during the study and 354 (28%) recurrences. Of the women with a recurrence, 306 (86%) died because of breast cancer and 21 (6%) died from other causes. There were 198 (16%) deaths from other causes in women without recurrence.

Patient characteristics and adherence. During the period from diagnosis to recurrence or death, 475 (38%) patients had low adherence to medication, missing at least one tablet of every five over the course of their therapy. The average monthly adherence index for our patients reduced over time from diagnosis from 85% (s.d. = 0.44) at 12 months to 81% (s.d. = 0.48) at 36 months and, finally, 75% (s.d. = 0.43) at 60 months.

The demographic and clinical characteristics of patients at diagnosis are shown in Table 1. A logistic regression model reported patients were more likely to have low adherence if they were younger women (OR = 0.26, 80+ *vs* <60 years, 95% CI: 0.15–0.45, $P<0.001$), had higher tumour stage (OR = 1.72, stage 3 or stage 4 *vs* stage 1 or 2, 95% CI: 1.10–2.67, $P=0.016$) or had ER-negative status (OR = 0.49, ER +ve *vs* ER −ve, 95% CI: 0.32–0.74, $P<0.001$) after controlling for menopausal status, social class, co-morbidity and other clinical characteristics.

Accelerated failure-time models for recurrence and death. For the 475 patients with low adherence to medication, 127 (27%) had a recurrence and 63 (13%) died before recurrence over the study period. For those with high adherence, 197 (25%) had a recurrence and 135 (17%) died before recurrence. Survival time from diagnosis to recurrence, diagnosis to recurrence-free death and recurrence to breast cancer death were calculated from a log-normal regression (see Table 2).

Table 1. Demographic and cancer characteristics at diagnosis by adherence

	Adherence				
	High (⩾80%) (*N* = 788), %		Low (<80%) (*N* = 475), %		*P*-value
Age group (years)					<0.001
<60	316	(40)	289	(61)	
60–69	214	(27)	98	(21)	
70–79	178	(23)	69	(15)	
80+	80	(10)	19	(4)	
Menopausal					0.005
Pre/Peri	64	(8)	59	(12)	
Post	262	(33)	135	(28)	
Unknown	462	(59)	281	(59)	
SIMD quintile					0.674
1–2 (Deprived)	228	(29)	132	(28)	
3–5 (Affluent)	548	(70)	335	(71)	
Unknown	12	(2)	8	(2)	
Charlson's index					0.527
0	340	(43)	216	(45)	
1–2	268	(34)	147	(31)	
3+	180	(23)	112	(24)	
Tumour stage					0.014
1–2	424	(54)	263	(55)	
3–4	56	(7)	57	(12)	
Unknown	308	(39)	155	(33)	
Axillary nodes					0.357
1	464	(59)	311	(65)	
2–3	78	(10)	62	(13)	
Unknown	246	(31)	102	(21)	
Metastases					0.570
No	545	(69)	371	(78)	
Yes	10	(1)	7	(1)	
Unknown	233	(30)	97	(20)	
Tumour grade					0.082
1–2	340	(43)	208	(44)	
3	173	(22)	136	(29)	
Unknown	275	(35)	131	(28)	
Oestrogen receptor status					<0.001
Negative	55	(7)	69	(15)	
Positive	389	(49)	239	(50)	
Unknown	344	(44)	167	(35)	

Abbreviation: SIMD = Scottish Index of Multiple Deprivation

The presence of involved axillary lymph nodes ($P<0.001$) and higher tumour grade ($P=0.001$) were each associated with shorter time to recurrence; age ($P<0.001$) and social class ($P=0.020$) with shorter time to recurrence-free death; and age ($P=0.007$) with shorter time from recurrence to breast cancer death after allowing for other factors. For patients with low adherence to tamoxifen, the expected time until recurrence reduced significantly by 52.38% ($P<0.001$), but there was no significant effect on time to other cause death or breast cancer death after recurrence.

Medical costs. Patients diagnosed at an older age ($P<0.001$), living in a deprived area ($P<0.001$) or with clinical metastases ($P=0.022$) were more likely to have costs within their subsequent follow-up years after adjusting for other factors (Table 3). Once

Table 2. Log-normal regression of the time to recurrence, other-cause mortality and breast cancer death after recurrence

From	Diagnosis				Recurrence	
To	Recurrence		Other cause death		Breast cancer death	
	Coefficient	P>z	Coefficient	P>z	Coefficient	P>z
Low adherence (<80%)	−0.5238	0.000	−0.2314	0.055	0.3349	0.161
Propensity score	−0.0948	0.241	−0.0611	0.303	−0.1284	0.453
Year of diagnosis	0.1108	0.006	0.0213	0.501	0.0835	0.207
Age group (reference <60), years						
60–69	−1.6128	0.206	−1.8726	0.048	−1.7643	0.444
70–79	−2.4296	0.134	−3.0279	0.011	−2.8490	0.379
80+	−3.6462	0.103	−3.7415	0.022	−4.3778	0.218
Menopausal (reference pre/peri)						
Post	−0.0378	0.895	−4.2405	0.973	−0.1661	0.721
Unknown	0.7762	0.078	−4.1833	0.973	0.2448	0.776
SIMD quintile (reference 1and 2: deprived)						
3–5 (Affluent)	0.2747	0.126	0.3055	0.020	0.3970	0.111
Unknown	−0.0725	0.924	0.1819	0.754	0.4298	0.682
Charlson's index (reference 0)						
1–2	−0.4042	0.142	−0.2352	0.226	−0.6477	0.540
3+	−0.2910	0.109	−0.0040	0.978	0.0973	0.781
Tumour stage (reference 1–2)						
3–4	0.7033	0.490	1.0442	0.156	1.6068	0.424
Unknown	0.4318	0.360	0.2477	0.456	0.6810	0.346
Axillary nodes (reference 1)						
2–3	−0.9710	0.000	0.2707	0.273	0.0615	0.839
Unknown	−1.2264	0.073	−0.4661	0.313	−0.7670	0.197
Metastases (reference no)						
Yes	−0.8591	0.186	−0.3906	0.415	0.0216	0.986
Unknown	−0.6088	0.238	0.0096	0.981	−1.1175	0.260
Tumour grade (reference 1–2)						
3	−0.7219	0.000	0.0349	0.839	−0.5842	0.144
Unknown	−0.0134	0.957	0.0716	0.687	−0.1282	0.823
Oestrogen receptor status (reference negative)						
Positive	−1.2131	0.384	−0.4607	0.642	−1.5521	0.579
Unknown	−0.8566	0.543	−0.7118	0.484	−1.4596	0.633

The reported coefficients refer to the rate by which the actual survival times increase with a unit increase in responding variables.

patients incurred some medical costs in a certain follow-up year, their costs were higher if they were older at diagnosis ($P<0.001$), living in a deprived area ($P=0.007$), lower tumour stage ($P=0.025$) or had node involvement ($P<0.001$). The results suggested that the first follow-up year and follow-up years with recurrence or death had significantly higher costs. Patients with low adherence were 37.05% less likely to have any costs ($P<0.001$), but once they had costs, these were expected to be 25.76% higher annually ($P<0.001$).

Outcomes, costs and the value of adherence. The summary statistics of the Markov models in terms of health outcomes and costs of tamoxifen for high and low adherence are presented in Table 4. High adherence was estimated to reduce recurrence by 8.95% (95% CI: −11.01 to −6.89%) and deaths from breast cancer by 8.65% (95% CI: −10.69 to −6.57%). High adherence was associated with expected further life years (LYs) of 14.78 and expected QALYs (discounted at 3.5%) of 11.43 compared with low adherence with 13.35 and 10.31, respectively.

Low adherence resulted in a loss of 1.43 LYs (95% CI: 1.15–1.71) or 1.12 QALYs (95% CI: 0.91–1.34). Over the expected lifetime, there was an incremental cost of £5970 for low *vs* high adherence (95% CI: −£7372 to −£4644) mainly due to the difference in in-patient stay and other dispensing costs.

As expected, high adherence to tamoxifen dominated low adherence with 100% of simulations showing it was both more effective and less costly than low adherence. Assuming a willingness to pay adoption threshold of £25 000 per QALY, the

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Table 3. Estimation results of the two-part models on annual medical costs

	1. Logit (non-zero costs)		2. ln (costs)	
	Coefficient	***P*>*z***	**Coefficient**	***P*>*t***
Low adherence (<80%)	−0.4629	0.000	0.2576	0.000
Propensity score	0.0905	0.414	0.0868	0.026
Follow-ups (reference Yr2+)				
Yr1			2.9177	0.000
Local recurrence			0.5496	0.159
Axiliary recurrence			1.5898	0.004
Distant recurrence			1.1649	0.000
Breast cancer death			2.2796	0.000
Other-cause death			1.9951	0.000
Year of diagnosis	0.0252	0.383	0.0097	0.491
Age group (reference <60), years				
60–69	1.6259	0.267	1.2613	0.016
70–79	3.3071	0.118	2.1157	0.004
80+	3.5656	0.125	2.6093	0.001
Menopausal (reference pre/peri)				
Post	0.3164	0.082	0.1541	0.119
Unknown	−0.1112	0.838	−0.3070	0.122
SIMD quintile (reference 1 and 2: deprived)				
3–5- affluent	−0.8081	0.000	−0.1402	0.007
Unknown	−0.7696	0.233	0.0462	0.858
Charlson's index (reference 0)				
1–2	0.8782	0.215	0.5497	0.022
3+	0.3064	0.069	0.0631	0.381
Tumour stage (reference 1–2)				
3–4	−1.2306	0.367	−1.0324	0.025
Unknown	−0.4610	0.291	−0.2107	0.186
Axillary nodes (reference 1)				
2–3	0.2379	0.218	0.3075	0.000
Unknown	0.9024	0.007	0.3007	0.031
Metastases (reference yes)				
No	−15.5193	0.022	−0.5763	0.075
Unknown	−15.6810	0.012	−0.1932	0.444
Tumour grade (reference 1–2)				
3	−0.3441	0.160	−0.0187	0.840
Unknown	−0.2229	0.470	−0.0340	0.780
Oestrogen receptor status (reference negative)				
Positive	1.6267	0.360	1.1324	0.073
Unknown	1.8644	0.341	1.2796	0.066
% Missing months	−1.0209	0.000	−0.0787	0.180

Coefficients in the first column capture how the probability a patient have non-zero costs within a year post cancer changes with variables; and coefficients in the second column capture, for patients with any costs within a year, how the amount of costs changes with variables.

expected value or NMB of changing a patient from low adherence to high adherence was £33 897 (95% CI: £28 322–£39 652).

Sensitivity analysis. Where the difference in costs between high and low adherence was only contributed to a higher chance of recurrence or other death, the incremental discounted cost of low adherence reduced to £1263 (95% CI: £204–£2361) and the NMB of high *vs* low adherence reduced to £29 161 (95% CI: £23 595–£34 715). When an alternative discount rate of 1.5% for outcomes was used, the incremental discounted QALYs of high adherence increased to 1.66 QALYs (95% CI: 1.32–2.00). The NMB equalled £47 501 (95% CI: £38 893, £56 160) if low adherence patients were assigned with

Table 4. Baseline and sensitivity analysis results for tamoxifen patients with high and low adherence

	Adherence		
	⩾80%	<80%	Difference (95% CI)
Baseline analysis[a] (Outcomes and costs discounted at 3.5%)			
Events (%)			
Recurrence	17.65%	26.59%	−8.94% (−11.01%, −6.89%)
Breast cancer death	17.32%	25.97%	−8.65% (−10.69%, −6.57%)
Effects (average per patient)			
LYs	14.78	13.35	1.43 (1.15, 1.71)
QALYs	11.43	10.31	1.12 (0.91, 1.33)
Costs			
Tamoxifen dispensing	£100	£56	£44 (£43, £45)
Inpatients and other dispensing	£14 747	£20 765	−£6014 (−£7416, −£4688)
Total costs	£14 847	£20 821	−£5970 (−£7372, −£4644)
Cost-effectiveness ratio			
Cost per LY gained			−£4239 (−£5583, −£3122)
Cost per QALY gained			−£5414 (−£7143, −£3993)
NMB of high *vs* adherence at £25 000/QALY			£33 897 (£28 322, £39 652)
Sensitivity analysis (costs)[b] (Outcomes and costs discounted at 3.5%)			
In-patients and other dispensing		£16 056	−£1307 (−£2405, −£247)
Total costs		£16 112	−£1263 (−£2361, −£204)
Cost per LY gained			−£894 (−£1700, −£145)
Cost per QALY gained			−£1142 (−£2172, −£185)
NMB of high *vs* adherence at £25 000/QALY			£29 161 (£23 595, £34 715)
Sensitivity analysis (effects) (Outcomes discounted at 1.5% and costs at 3.5%)			
LYs	20.10	17.98	2.12 (1.69, 2.56)
QALYs	15.57	13.91	1.66 (1.32, 2.00)
Cost per LY gained[a]			−£2871 (−£3793, −£2108)
Cost per QALY gained[a]			−£3670 (−£4838, −£2694)
NMB of high *vs* adherence at £25 000/QALY[a]			£47 501 (£38 893, £56 160)
Cost per LY gained[b]			−£604 (−£1150, −£113)
Cost per QALY gained[b]			−£772 (−£1469, −£144)
NMB of high *vs* adherence at £25 000/QALY[b]			£42 861 (£34 550, £51 266)

Abbreviations: LY = life year; NMB = net monetary benefit; QALY = quality-adjusted life year.
[a]Assume annual costs of in-patients and other dispensing differ between high-adherence and low-adherence patients.
[b]Assume low-adherence patients bear the same annual costs of in-patients and other dispensing as high-adherence patients (predictions are made based on high-adherence patients).

different annual costs and £42 861 (95% CI: £34 550, £51 266) otherwise. The results were robust with high adherence dominating in at least 95% of simulations throughout all sensitivity analyses.

DISCUSSION

Within 5 years from diagnosis, approximately two-fifths of women prescribed tamoxifen had adherence less than 80%, which was associated with significantly shorter time to recurrence and significantly higher health service costs, once costs were incurred. Assuming the current value of a QALY is £25 000, the expected value of changing a patient from low to high adherence was £33 897 (95% CI: £28 322–£39 652).

This study provides empirical evidence, which suggest the importance of improving adherence to adjuvant tamoxifen in community settings and also indicates the potential benefits of investing in adherence to enhance health outcomes and economic efficiency.

Furthermore, we demonstrate that younger patients were more likely to have lower adherence, whereas the patients' tumour stage and status of ER are also significantly associated with adherence behaviour.

Comparison to the literature. This study supports published literature showing that a large proportion of women have low adherence over the 5 years following diagnosis (Barron *et al*, 2007; Ma *et al*, 2008; McCowan *et al*, 2008; Owusu *et al*, 2008; Yood *et al*, 2008; Narod, 2010; van Herk-Sukel *et al*, 2010; Hershman *et al*,

2011; Murphy *et al*, 2012; Hadji *et al*, 2013; Huiart *et al*, 2013; Makubate *et al*, 2013). For those women with low adherence, there is an increased risk of poor health outcomes, although the association with other-cause mortality was not significant (Patridge *et al*, 2003; McCowan *et al*, 2008; Dezentje *et al*, 2010; Hershman *et al*, 2010, 2011; Makubate *et al*, 2013).

Although no previous studies were identified that had performed an economic analysis of adherence to tamoxifen, the finding that low adherence was associated with higher costs and lower quality of life fits well with the studies reporting the cost-effectiveness of tamoxifen use (Glasziou and Haas, 1994; Yang *et al*, 2010). We report a higher difference of QALYs than the original Australian study, but have confirmed the direction of effect with our increased difference possibly due to differences in the underlying populations and groupings within the two studies. The findings also relate well to a study of the cost-effectiveness of statins, which reported that improving adherence to medication would enhance cost-effectiveness (Greving *et al*, 2011).

This study provides direct evidence that low adherence to long-term oral breast cancer therapy results in poor health outcomes and increased health costs. This has become a growing concern as shown by the calls to develop interventions that improve adherence, as such interventions might have a greater impact on population health than improvements in specific medical treatments (Sabaté and World Health Organization, 2003).

Implications for practice. The adherence behaviour of patients is a complex process determined by many factors (Osterberg and Blaschke, 2005; Ruddy *et al*, 2009). Besides patient-related factors, the characteristics of the disease and its treatment, the attributes of the health-care system and service delivery may also influence adherence (Murphy *et al*, 2012; Hadji *et al*, 2013). It may be difficult to identify patients who will have low adherence until that behaviour is established and it is also likely that no single approach will be successful. There is a need for studies on the design of interventions that improve adherence more effectively (Sabaté and World Health Organization, 2003; Murphy *et al*, 2012). Clinicians currently supporting women receiving adjuvant therapy for breast cancer should specifically ask about adherence and increase the support they offer to encourage more women to complete their full course of medication.

Strengths and limitations. The study was based on women managed within the community and used actual health service resource use allocation to inform the economic evaluation. The initial population comprised all breast cancers diagnosed from an entire population with exclusions based on well-described criteria. Although measuring adherence to medication is complex, we used an established method. The dispensed prescribing records were from a closed prescribing system with every prescription presented to a pharmacist recorded and collated and these data were then linked to health board wide population databases including cancer registry and official death certificates.

We applied a propensity score method to reduce the potential selection bias of low adherence when modelling health outcomes and medical costs: patients who have low adherence to tamoxifen may have poor health prospects, and in addition, they may prefer to use less health resources, which may induce more health-care costs later on when their condition worsens. However, a sensitivity analysis reported consistent results when low-adherence patients were assigned with the same predictions on other annual costs as if they had high adherence.

We excluded a 60-day period before death or recurrence in our calculations of adherence to allow for the possibility that patients may stop taking medications as they approached either. A longer exclusion period may modify the results but we felt that a two-month window was a sufficient period. Our adherence measure included women with poor persistence who had stopped taking medication before completing a 5-year course or having a recurrence or death. Our study numbers are insufficient to disentangle whether patient who take drugs regularly but for a shorter period than recommended have different outcomes from those who take the drugs for longer periods of time but at less regular intervals. However, our focus was on whether adherence to recommended treatment improved patient and economic outcomes. We used data from a Swedish population to estimate QALYs, as this was the most reliable data available for our study and also represents a similar, predominantly Caucasian population in a socialised health-care system (Lidgren *et al*, 2007). Our use of an average cost for prescriptions other than tamoxifen when estimating patient costs has limitations, but as we would have been unable to attribute which medications were used specifically for breast cancer or associated conditions, we felt this was a suitable assumption within our study.

Our focus was limited to adherence in tamoxifen patients given the sampling period and duration of follow up. A further evaluation comparing the impact of adherence to AIs compared with tamoxifen adjuvant endocrine therapy is necessary. However, such analyses should be confined to post-menopausal women, whereas the current study examined women of all ages. As evidence emerges for the long-term benefits of adjuvant tamoxifen beyond 5 years, specifically the trials comparing 10 years *vs* 5 years adjuvant tamoxifen (and similar duration trials for AIs), the issues around adherence will become even more critical for the long-term health and economic impacts of breast cancer therapy.

CONCLUSION

The consequences of low adherence to tamoxifen are poorer health outcomes, increased health-care costs and worse quality of life. Interventions that encourage patients to continue taking their treatment on a daily basis for the recommended 5-year period should improve outcomes and may be highly cost-effective, with the investment justified by better health outcomes and savings in reduced health-care utilisation.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf; the authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CMcC and AMT conceived the study and supported DJP and SW who planned the study. SW carried out the analysis with support from DJP, BM and CMcC. All authors contributed to the writing of the paper. CMcC is the guarantor.

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