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Clinical consultations and investigations before and after discontinuation of endocrine therapy in women with primary breast cancer

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Key points

- Previous research shows that 58% of Australian women using endocrine therapy for primary invasive breast cancer discontinued treatment before the recommended 5 years
- We find no evidence to suggest that early discontinuation of endocrine therapy is associated with recent clinical contact or investigations for cancer recurrence or metastasis
- Women who discontinue endocrine therapy early are less likely to consult their general practitioner or surgeon/oncologist in the 6 months following discontinuation than those who remained on therapy

Abstract

Objective: Although clinical trials recommend that women with hormone-dependent primary breast cancer remain on endocrine therapy for at least 5 years, up to 60% discontinue treatment early. We determined whether these women had consulted with clinicians or had investigations for cancer recurrence or metastasis around the time they discontinued endocrine therapy, and whether clinical contact continued after discontinuation.

Methods: We performed case-control and cohort studies of women from the 45 and Up Study who were diagnosed with invasive primary breast cancer between January 2003 and December 2008, and who had ≥ 12 months of anastrozole, exemestane, letrozole or tamoxifen subsequently dispensed.

Results: Women who consulted general practitioners and surgeons/oncologists, and women who had breast ultrasound/mammogram were just as likely to discontinue endocrine therapy within 30 days as those who did not consult these clinicians or have this investigation. In the 6 months after early discontinuation, women who discontinued endocrine therapy were less likely to consult general practitioners (adjusted risk ratio [RR_{adj}] 0.80; 95% confidence interval [CI] 0.75, 0.86) and surgeons/oncologists (RR_{adj} 0.62; 95% CI 0.54, 0.72) than those who remained on therapy.

Conclusions: For most women, endocrine therapy discontinuation did not appear to follow consultation with doctors managing their breast cancer treatment or investigations for recurrence or metastasis. However, women who discontinued endocrine therapy were less likely to consult their general practitioner or surgeon/oncologist in the 6 months following discontinuation than those who remained on therapy. Of the clinician groups studied, general practitioners are best placed to engage and support women to continue pharmacotherapy. However, mechanisms are needed to prompt clinicians to do this at every visit.

Introduction

Endocrine therapy is an established adjuvant treatment for women with hormone-dependent primary breast cancer.¹ Despite clinical trials showing that endocrine therapy halves the risk of recurrence and reduces cancer-related mortality when taken for at least 5 years²⁻⁶, many women discontinue treatment early^{7,8}, leaving them at an increased risk of cancer recurrence and death.^{8,9} We have previously shown that 58% of Australian women using endocrine therapy for primary invasive breast cancer discontinued treatment before the recommended 5 years.¹⁰ We were interested to determine if these women consulted with clinicians or had investigations for cancer recurrence or metastasis performed at or around the time the decision to discontinue endocrine therapy was made. This may reflect clinical consultation and decision making relating to issues such as side-effect management or continuing benefit of pharmacotherapy. In addition, we examined whether clinical follow-up continued after endocrine therapy discontinuation.

We hypothesised three possible relationships between discontinuation of endocrine therapy and clinical contact or investigations performed. Firstly, discontinuation may follow consultation with doctors managing the women's breast cancer treatment or side effects of endocrine therapy (e.g. musculoskeletal pain). Secondly, discontinuation may follow negative test results (i.e. 'good news') from screening for recurrence or metastasis. Thirdly, discontinuation may co-occur with loss of clinical follow-up after discontinuing therapy. Understanding this relationship is important to design appropriate interventions to support women to continue endocrine therapy for the recommended period. For example, if discontinuation is associated with negative screening test results for either local or distant disease, then an appropriate intervention, such as encouragement and reinforcement of the benefits of continuing endocrine therapy, could be provided by the clinician when patients receive this news.

If clinical consultation and investigations are not related to discontinuation, this may suggest that clinicians are unaware of a woman's endocrine therapy status and that every clinical contact is an important opportunity to re-emphasise the importance of maintaining endocrine therapy and support patients to maintain use. Accordingly, the aim of this study was to determine whether women receiving endocrine therapy for primary breast cancer had an outpatient clinician visit or investigation for cancer recurrence and metastasis in the weeks before endocrine therapy discontinuation, and if clinical follow-up occurred after discontinuation.

Methods

We conducted case-control and cohort studies using administrative linked data and survey data of women from the 45 and Up Study who commenced endocrine therapy for primary breast cancer.

Primary study base

Participants were drawn from the Sax Institute's 45 and Up Study, a cohort of about 267 000 adults (143 014 women) in New South Wales (NSW), Australia, aged ≥ 45 years.¹¹ Participants joined the study between January 2006 and April 2009, and completed a detailed baseline questionnaire of demographic, behavioural and health-related items. All participants recruited to the 45 and Up Study also provided written informed consent to have their health claims data that are routinely collected by the Australian Government Department of Human Services linked, and for these data to be provided to third-party researchers for approved projects.

Data sources and linkage

We accessed unit-record, linked data from: 1) the 45 and Up Study baseline survey; 2) NSW Admitted Patient Data Collection (hospital data); 3) NSW Cancer Registry; 4) Medicare Benefits Schedule (MBS) claims; 5) Pharmaceutical Benefits Scheme (PBS) claims; and 6) NSW Registry of Births Deaths & Marriages. PBS and MBS data were supplied by the Department of Human Services and deterministically linked to the 45 and Up Study baseline data. The remaining datasets were probabilistically linked by the NSW Centre for Health Record Linkage¹², with quality audits showing fewer than 0.5% false positive links.¹³ The study period was from 1 January 2003 to 30 November 2011.

Study participants

Participants drawn from the primary study base for this study were women with a diagnosis of invasive primary breast cancer on the NSW Cancer Registry between January 2003 and December 2008, and who had ≥ 12 months of PBS-subsidised anastrozole, exemestane, letrozole or tamoxifen subsequently dispensed. Furthermore, to allow a 1 year follow-up after discontinuation, women were excluded if they discontinued endocrine therapy after 31 October 2010. Although there was increasing use of an aromatase inhibitor at some point in the treatment during this time, overall there was no change in the recommendation to use endocrine therapy in the study period.

Selection of cases and controls

Cases were defined as women who had commenced endocrine therapy after diagnosis and subsequently had no dispensing of endocrine therapy for a period greater than 180 days ('discontinuation') before the end of follow-up (cancer recurrence, death, end of study period, or 4 years of therapy – whichever occurred first).¹⁰ Women who switched endocrine therapy treatment (e.g. tamoxifen to letrozole) before the end of follow-up were not classified as cases. The date of discontinuation was the last recorded dispensing date plus the supply period.¹⁰ We excluded women who discontinued endocrine therapy after 4 years

because clinical concern would be greatest for those who stopped before this time and discontinuation after 4 years may have been planned.

Each case was randomly assigned to one control (defined as women with primary breast cancer who did not discontinue endocrine therapy during follow-up). Because each woman had a different endocrine therapy initiation date, and to ensure comparable follow-up periods, we assigned pseudo-discontinuation dates to each control based on the duration on endocrine therapy of their randomly assigned case.¹⁴

Given the inclusion criteria described, we identified 261 cases, and sufficient cases and controls for a 1:1 match.

Ascertainment of side effects, recurrence and death

Ascertainment of endocrine therapy side effects, recurrence and death in this cohort has been described in detail previously.¹⁰ In brief, dispensing of medicines used to treat anxiety, depression, hot flushes, musculoskeletal pain, osteoporosis and vaginal atrophy observed only after initiation of endocrine therapy were used to identify new-onset side effects. Breast cancer recurrence was identified from: 1) specified surgeries (lumpectomy, mastectomy, oophorectomy), chemotherapy and radiotherapy occurring for the first time >18 months from the date of diagnosis or >12 months after previous claims for these events; or 2) first dispensing of medicines (capecitabine, lapatinib, medroxyprogesterone, megestrol, toremifene, vinorelbine) indicated only for advanced breast cancer. Date of death was ascertained from the NSW Registry of Births Deaths & Marriages.

Ascertainment of clinical consultations and investigations

Specified clinical consultations and investigations were selected after expert clinical consultation to derive the most appropriate services to analyse to test our hypothesised relationships. Clinical contacts of interest included consultations with general practitioners and outpatient consultations with oncologists, surgeons, rheumatologists or gynaecologists during the 30 days before discontinuation of endocrine therapy (Supplementary Table 1, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). These were ascertained from the MBS data.

Investigations related to screening for cancer recurrence (namely mammogram or breast ultrasound) and metastasis (isotope bone scan or fluorodeoxyglucose positron emission tomography [FDG-PET] or computed tomography [CT] scan) performed up to 30 days before discontinuation of endocrine therapy were also ascertained from the MBS data (Supplementary Table 2, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). All post-breast cancer

mammograms in NSW are done with Medicare rebates and recorded in the MBS data. To determine if women had clinical follow-up after discontinuation, we followed them for 6 months after discontinuation. Most prescriptions provide a supply for up to 6 months, and an earlier study showed that most breast cancer patients attend consultations every 6 months.¹⁵

Other covariates

Residential location, annual household income, highest level of education and country of birth were reported by participants at recruitment to the 45 and Up Study. Residential location was coded using the Accessibility/Remoteness Index of Australia.¹⁶ Cancer stage was determined from the NSW Cancer Registry. We calculated the number comorbidities using the Australian modification of Rx-Risk-V, a prescription-based comorbidity index, and using person-level data from PBS claims for 12 months before discontinuing endocrine therapy.^{17,18} We excluded malignancy from the comorbidity count because all women had a history of malignancy. Concession card status was determined because the PBS dataset did not capture dispensing to general beneficiaries (i.e. nonconcession cardholders) when the medicines cost less than the copayment.¹⁹

Statistical analysis

We initially used t-tests and chi-square tests to compare continuous and categorical characteristics, respectively (demographic and clinical), of cases and controls. For the analyses of previous clinical contacts and investigations for cancer recurrence on endocrine therapy discontinuation, a case-control study design was used. For these, multivariate conditional logistic regression analyses were used to determine the adjusted odds ratio (OR_{adj}) of discontinuing endocrine therapy within 30 days following exposure to specified clinical contacts and investigations for cancer recurrence.

For analyses on clinical contacts following endocrine therapy discontinuation, a cohort study design was used. For these, multivariate Poisson regression analyses were used to determine the likelihood of cases having clinical contact in the 6 months following discontinuation compared with controls. With binary outcomes, the exponentiated coefficients from the multivariate Poisson regression represent adjusted risk ratios (RR_{adj}) rather than incidence rate ratios.^{20,21} We used risk ratios because odds ratios are biased estimators of risk when the prevalence is high for the outcome being investigated (e.g. general practitioner consults).

All models were controlled for a range of covariates, including age at endocrine therapy discontinuation, highest level of education, annual household income, area of residence, country of birth, stage, number of comorbidities, concession card status, family history of breast cancer and new-onset side effects. Because women with new-onset side effects could be more likely to consult a clinician

to manage these problems, we included the interaction term “discontinued endocrine therapy*new-onset side effect” in regression analyses for clinical consults to determine if there was any effect modification. We also assessed the interaction term “discontinued endocrine therapy*concession card” as the likelihood of clinical consultations may differ between those on concession and general beneficiaries. Aggregated counts of less than five were masked (presented as <5) to protect patient confidentiality. Analyses were performed using Stata.

Ethics statement

This study was conducted in accordance with Australian law. The consent procedure for entry to the 45 and Up Study was approved by the University of NSW Human Research Ethics Committee and the Australian Government Department of Health. The current study also received approval from the University of Western Australia Human Research Ethics Committee (approval RA/4/1/4589), and the NSW Population and Health Services Research Ethics Committee (approval HREC/11/CIPHS/35).

Results

Demographic and clinical characteristics of cases and controls

Of the 1531 women who commenced endocrine therapy, we identified 261 cases who discontinued endocrine therapy after 1–4 years (median duration 1.8 years) of therapy. Cases and controls were similar in age, highest level of education attained, annual household income, area of residence, concession card status, number of comorbidities, family history of breast cancer and new-onset side effects (Supplementary Table 3, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). There were marginally more Australian-born women in the control than the case group (77.0% vs 71.6%, $p = 0.037$). Fewer than 10 women (<3.8%) in the case and control groups were lost to follow-up because of death in the year following endocrine therapy discontinuation. In the control group, similar numbers of women had localised and regionalised cancers (47.5% vs 48.7%, respectively), whereas in the cases there were more women with localised than regionalised cancers (62.8% vs 33.0%, respectively).

Endocrine therapy discontinuation within 30 days of specified clinical consultations

Similar numbers of cases and controls consulted with general practitioners (43.7% vs 44.8%, $p = 0.791$), surgeons/oncologists (16.9% vs 14.2%, $p = 0.397$) and rheumatologists/gynaecologists (3.1% vs <1.9%, $p = 0.243$) in the 30 days before endocrine therapy discontinuation (Supplementary Table 4, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). In the

fully adjusted regression models, women who consulted general practitioners (OR_{adj} 0.91; 95% CI 0.62, 1.33) and surgeons/oncologists (OR_{adj} 1.44; 95% CI 0.87, 2.41) had similar odds of discontinuation within 30 days as those who did not consult these clinicians. Women who consulted rheumatologists/gynaecologists were 3.03 times (95% CI 0.72, 12.69) more likely to discontinue within 30 days than those who did not consult this type of specialist, but they represent <5% of women and this was not statistically significant. Adjusted odds ratios for general practitioner and surgeon/oncologist consults were similar to their unadjusted estimates.

Endocrine therapy discontinuation within 30 days of specified clinical investigations

Similar numbers of cases and controls discontinued endocrine therapy within 30 days of having a breast ultrasound/mammogram (6.5% vs 8.4%, $p = 0.405$). However, twice the number of cases had bone study/FDG-PET/CT scan than controls (5.7% vs 2.7%, $p = 0.081$) (Supplementary Table 5, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). In the multivariate analyses, there were no significant differences in the odds of discontinuing endocrine therapy within 30 days in women who had a breast ultrasound/mammogram (OR_{adj} 0.73; 95% CI 0.37, 1.44) and bone study/FDG-PET/CT scan (OR_{adj} 2.13; 95% CI 0.80, 5.70) compared with women who did not have these investigations. Adjusted odds ratios for these clinical investigations were similar to their unadjusted estimates.

Consultations in the 6 months following endocrine therapy discontinuation

In the 6 months following endocrine therapy discontinuation, fewer cases than controls had consulted with general practitioners (79.3% vs 97.3%, $p < 0.001$) and surgeons/oncologists (48.3% vs 78.9%, $p < 0.001$) (Supplementary Table 6, available from: researchdataonline.research.uwa.edu.au/handle/123456789/3001). Similar but small numbers had consulted a rheumatologist or gynaecologist (9.2% vs 8.8%, $p = 0.878$). In the multivariate model, women who discontinued endocrine therapy were less likely to consult general practitioners (RR_{adj} 0.80; 95% CI 0.75, 0.86) and surgeons/oncologists (RR_{adj} 0.62; 95% CI 0.54, 0.72). The interaction terms “discontinuing endocrine therapy*new-onset side effects” and “discontinuing endocrine therapy*concession card” were not significant in the regression analyses for outcomes relating to general practitioner, surgeon/oncologist and rheumatologist/gynaecologist consults.

Discussion

We were interested to determine whether women with a diagnosis of primary breast cancer who discontinued endocrine therapy within 4 years of treatment initiation

had consulted clinicians, or had investigations for cancer recurrence or metastasis at or around the time they discontinued pharmacotherapy. Such information would help to contextualise the high levels of early endocrine therapy discontinuation that have been reported^{7,8,22-25} in terms of clinical contact and investigations performed. We found that women who consulted general practitioners and surgeons/oncologists, and women who had breast ultrasound/mammogram were just as likely to discontinue endocrine therapy within 30 days as those who did not consult these clinicians or have this investigation. Women who discontinued endocrine therapy were less likely to consult general practitioners and surgeons/oncologists in the 6 months following discontinuation.

We did not find any evidence to suggest that women discontinued endocrine therapy following recent clinical contact or investigations related to recurrence or metastasis. Encouragingly, many women continued to consult clinicians (especially general practitioners) after early discontinuation, although they were less likely to do so than those who continued endocrine therapy. This perhaps emphasises the need for every clinical contact, including those where investigation results are discussed, to be used as an opportunity for discussion with the patient about the importance of ongoing endocrine therapy for at least the first 5 years (as is recommended in current clinical guidelines²⁻⁶) or possibly longer (more recent data supports endocrine therapy use for 10 years²⁶). Importantly, a recent qualitative study of breast cancer patients in the UK found that healthcare professionals did not routinely or systematically monitor the patient's adherence to endocrine therapy, and few women reported having the opportunity to discuss side effects or the potential options available with their clinician.²⁷ Kostev et al. suggest that, for women to remain on endocrine therapy, clinicians need to clearly communicate the seriousness of the condition, the importance of the treatment and its potential side effects, and motivate the patient to take the medicine as prescribed.²⁸

Of the three groups of clinicians investigated here, general practitioners are arguably best placed to encourage and support women with their endocrine therapy. Most (79%) women who discontinued endocrine therapy had consulted their general practitioner in the 6 months following discontinuation, which was considerably higher than seen for other clinician types. The role of the general practitioner is even more important in rural and remote areas because women living in these areas have limited access to cancer specialists.²⁹ General practitioner contact is likely to be more regular and frequent than specialist consultations, and therefore provides more opportunity to support endocrine therapy. On the other hand, there may be other competing issues for care (e.g. management of other chronic conditions) when women contact their general practitioner. Given time constraints, the general practitioner may be likely to focus on the condition related

to the patient's reason for contact and may overlook the ongoing breast cancer pharmacotherapy regime, especially if it has been a number of years since the initial treatment. There needs to be mechanisms in general practice to prompt the clinician to engage and motivate these women to continue pharmacotherapy at every visit, and to contact women who have not had a recent consult. Consideration could also be given to engaging pharmacists in activity to support persistence with therapy, as all repeat dispensing for endocrine therapy is provided by the pharmacy.

In advocating for more clinician engagement and motivation, we are assuming that the decision to discontinue endocrine therapy was made solely by the patient. However, one study using self-reported data showed that the decision to discontinue endocrine therapy early was made with the clinician in 65% to 74% of women who discontinued.³⁰ It is possible there was underreporting of self-initiated discontinuation, underascertainment of cancer recurrence (as a reason for discontinuation), or that women may have misunderstood the discussion they had with their doctor given the self-reported information used. A qualitative study of 30 women found that three women had discontinued endocrine therapy based on the decision of their clinician as they were considered to be low risk for cancer recurrence.²⁷ However, this study did not indicate if the women stopped because they were nearing 5 years since treatment initiation.

Strengths and limitations

To our knowledge, this is the first study to examine clinical consultations and investigations before and after discontinuing endocrine therapy. We used administrative medical records for a heterogeneous population-based community sample for which all publicly subsidised endocrine therapy, outpatient consultations and clinical investigations were captured. We did not have access to the women's clinical notes and therefore could not ascertain the reason for consultation, the details of the clinician-patient discussion that took place or the outcome of the consultation. We are likely to have underascertained the number of comorbidities in nonconcession cardholders, as certain medications are below copayment.¹⁹ However, as the distribution of concession cardholders and number of Rx-Risk comorbidities were similar in both cases and controls, we do not expect any bias in the results. The sample for this study was drawn from the 45 and Up Study, limiting the sample to women aged ≥ 45 years and consenting to linkage of their health records. Their health service history may differ from younger women or those who did not agree to participate in cohort studies. Given the small sample size, the results should be interpreted with caution.

Conclusions

The evidence does not support the hypothesis that early endocrine therapy discontinuation is associated with recent clinical contact or investigations for cancer recurrence or metastasis. However, women who discontinued endocrine therapy were less likely to consult a clinician in the 6 months following discontinuation. Clinical contact cannot be assumed to support persistence with pharmacotherapy. Every consultation should be used as an opportunity to look into the women's breast cancer management. Of the clinician groups studied, general practitioners are best placed to engage and support women to continue pharmacotherapy. However, there needs to be mechanisms in place to prompt clinicians to do this at every visit and to contact women who have not had a recent consult.

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Competing interests

None declared

Author contributions

AKC, CS, FB, ER and DP conceived the study and interpreted data. DL performed the statistical analyses and drafted the manuscript. MB aided with data interpretation and critically reviewed the statistical content of the manuscript. DP, CS, FB and MB assisted with acquisition of data and critically reviewed the manuscript. All authors read and approved the final manuscript and are accountable for all aspects of the work.

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