Improving outcomes for women aged 70 years or above with early breast cancer: research programme including a cluster RCT

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/XZOE2552.

Primary conflicts of interest: Lynda Wyld reports membership of the National Institute for Health and Care Research (NIHR) Surgery Themed Call Board (3 October 2012–13 March 2013). Jenna Morgan reports being a NIHR Clinical Lecturer funded by NIHR. Stephen Walters reports membership of the Health Technology Assessment (HTA) Funding Committee Policy Group (28 May 2012–30 November 2017) and HTA Clinical Evaluation and Trials Committee (18 August 2010–30 November 2017). His main employer (School for Health and Related Research, University of Sheffield) has contracts and/or research grants with the Department of Health, NIHR, Medical Research Council (MRC) and the National Institute for Health and Care Excellence (NICE). He is a co-applicant or co-investigator on several NIHR portfolio grants [HTA, Public Health Research (PHR) and Efficacy and Mechanism Evaluation (EME) programmes, and Research for Patient Benefit (RfPB)] and grants from the MRC. He is a NIHR Senior Investigator and funded by the NIHR. He reports grants from other research grants, personal fees from book royalties and grants from the NIHR Senior Investigator Award outside the submitted work. Alistair Ring reports personal fees from F. Hoffman-La Roche Ltd (Basel, Switzerland), Novartis Pharmaceuticals UK Ltd (London, UK), Pfizer Inc. (New York, NY, USA), Eli Lilly and Company (Indianapolis, IN, USA) and Merck & Co. Inc. (Kenilworth, NJ, USA) outside the submitted work. Esther Herbert reports grants from NIHR during the conduct of the study (the Age Gap study). Thompson G Robinson is a NIHR Senior Investigator. Nicolo Matteo Luca Battisti reports grants from Genomic Health, Inc. (Redwood City, CA, USA), and grants and personal fees from Pfizer Inc. outside the submitted work. Margot Gosney reports membership of the HTA Prioritisation Committee A (1 November 2013–28 February 2019) and the HTA Elective and Emergency Specialist Care (EESC) Panel (1 November 2013–31 May 2018). Matt Winter reports personal fees and non-financial support from Easai Co., Ltd (Tokyo, Japan), personal fees from Pfizer Inc., personal fees and non-financial support from Eli Lilly and Company, personal fees from Genomic Health, Inc./Exact Sciences Corporation (Madison, WI, USA), personal fees from Novartis Pharmaceuticals UK Ltd and personal fees and non-financial support from F. Hoffman-La Roche Ltd outside the submitted work.

Published June 2022
DOI: 10.3310/XZOE2552

Scientific summary

Bridging the Age Gap in Breast Cancer research programme

Programme Grants for Applied Research 2022; Vol. 10: No. 6
DOI: 10.3310/XZOE2552

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

In breast cancer management, age-related practice variation is widespread, with older women having lower rates of surgery and chemotherapy than younger women, based on the premise of reduced treatment tolerance and benefit. This may contribute to inferior outcomes. There are no age- and fitness-stratified thresholds on which to base treatment recommendations or to support decision-making in this older age group of women with early-stage breast cancer.

Aims

- To optimise treatment and outcomes for older women with operable breast cancer by determining composite age, tumour and fitness thresholds for treatment selection and patient benefit.
- To develop, validate and trial an older-age-specific decision support intervention (DESI) to support the shared decision-making of older women in the UK facing treatment choices for their breast cancer.

Objectives

- To determine the age, comorbidity, frailty, disease stage and biology thresholds for primary endocrine therapy (ET ALONE) versus surgery plus adjuvant endocrine therapy (S+ET), or adjuvant chemotherapy versus no chemotherapy for older women.
- To optimise outcomes [overall survival (OS), breast-cancer-specific survival (BCSS) and quality of life (QoL)] for older women.
- To develop and evaluate a DESI to support treatment choices.
- To determine the degree and causes of treatment variation between UK breast units.

Design

A prospective cohort study was used to determine age and fitness thresholds for treatment allocation. A large multicentre UK cohort of older women, aged $\geq$ 70 years, with operable breast cancer was recruited. The aim was to use the existing variation in selection criteria for ET ALONE versus S+ET, or adjuvant chemotherapy versus no chemotherapy, to derive a matched cohort of women for each comparison. This facilitated propensity score matching to reduce the bias innate in observational cohort studies, allowing comparison of outcomes from these treatments. Previous attempts to run randomised trials in this age group to compare S+ET with ET ALONE [the Endocrine $\pm$ Surgical Therapy for Elderly women with mammary cancer (ESTEEM) trial] or adjuvant chemotherapy with no chemotherapy [the adjuvant chemotherapy in older women (ACTION) trial] had both failed to recruit owing to lack of clinician and patient equipoise (Reed MW, Wyld L, Ellis P, Bliss J, Leonard R; ACTION and ESTEeM Trial Management Groups. Breast cancer in older women: trials and tribulations. *Clin Oncol* 2009;**21**:99–102.).

Mixed-methods research was used to determine the information needs of older women and to inform the development of a DESI. This would allow us to determine the optimal information content and format for displaying that information to meet the needs of older women facing a choice of S+ET or ET ALONE, or whether or not to have adjuvant chemotherapy. A series of qualitative interviews were performed to explore these issues and quantification of preferences was performed using a larger questionnaire survey.

An evidence summary was also derived using systematic literature review methodology. All of these data sources were then used to develop and pilot two DESIs specifically for older women facing these choices.

A cluster-randomised trial was used to evaluate the impact of these DESIs on treatment choices and outcomes. This was conducted at the same centres that had been recruiting to the cohort study, so sites were familiar with the data collection methods; this allowed rapid trial adoption and set-up. The centres were cluster randomised to either continue with their usual patient counselling methods to support the two treatment choices (S+ET vs. ET ALONE, or adjuvant chemotherapy vs. no chemotherapy), or to have training in and access to the two DESIs.

Health economic analysis was performed using a mixture of data sources, including registry data, published data about treatment allocations and outcomes, and data from the Age Gap cohort study. Health utility data were taken from published sources. A partitioned survival model was created. The primary analysis was a cost–utility analysis, which estimated the lifetime health outcomes achieved, measured in quality-adjusted life-years (QALYs), and the health service costs incurred for patients receiving the two alternative treatment options (S+ET and ET ALONE).

A mixed-methods study was used to determine the extent and causes of variation in treatment allocation. This analysis was conducted on both UK registry data and the Age Gap cohort data. Rates of surgery were compared between centres and also between individual consultants and adjusted for case mix to determine whether or not rates varied significantly. Qualitative interviews and a questionnaire survey were also performed to gain insight into the reasons for this variation.

Main outcome measures

- Establish thresholds for fitness-stratified treatments to improve outcomes in older women (≥ 70 years) with breast cancer using a range of measures (survival, QoL and cost-efficacy).
- Enhanced shared decision-making for older women facing treatment choice by development and trialling of DESIs.

Results

Cohort study

The study recruited 3416 women (median age 77 years). Follow-up was 52 months.

Surgery plus adjuvant endocrine therapy versus primary endocrine therapy comparison

A total of 2854 out of 3416 (88%) women had oestrogen-receptor-positive (ER+) breast cancer: 2354 received S+ET and 500 received ET ALONE. Patients treated with ET ALONE were older and frailer than patients treated with S+ET. Unmatched OS and BCSS were higher in the S+ET group than in the ET ALONE group [OS: hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.23 to 0.33; $p < 0.001$; BCSS: HR 0.41, 95% CI 0.29 to 0.58; $p < 0.001$). In the matched analysis, S+ET was still associated with better OS than ET ALONE (HR 0.72, 95% CI 0.53 to 0.98; $p = 0.04$), but not with better BCSS (HR 0.74, 95% CI 0.40 to 1.37; $p = 0.34$) or progression-free survival (HR 1.11, 95% CI 0.55 to 2.26; $p = 0.78$).

Analysis of QoL outcomes found that type of surgery was associated with different levels of QoL impairment following major surgery; for example, mastectomy had a significantly greater negative impact than wide local excision, and axillary surgery had a significantly greater negative impact than sentinel node biopsy. Similarly, major surgery had a greater negative effect than ET ALONE, with little difference between minor surgery and ET ALONE. In a propensity-matched cohort of women (matched for age, health, frailty and tumour stage), women having major surgery had significantly worse arm symptoms [mean difference (MD) 8.85, 95% CI 3.63 to 14.07] than ET ALONE patients, and the symptoms did not return to baseline even at 2 years.

Adjuvant chemotherapy versus no chemotherapy comparison

A total of 2811 out of 3416 (82%) women in the cohort underwent surgery, of whom 1520 (54%) had high-recurrence-risk breast cancer [oestrogen receptor negative (ER–), human epidermal growth factor receptor-2 positive (HER-2+), grade 3, node positive or an Oncotype DX® (Genomic Health, Inc., Redwood City, CA, USA) score of > 25]. In this high-risk population, there were no differences in OS or BCSS according to adjuvant chemotherapy use after propensity matching. Adjuvant chemotherapy was associated with a lower risk of metastatic recurrence in the unmatched (adjusted HR 0.36, 95% CI 0.19 to 0.68; $p = 0.002$) and propensity-matched patients (adjusted HR 0.43, 95% CI 0.20 to 0.92; $p = 0.03$). Adjuvant chemotherapy improved OS and BCSS in patients with ER– disease.

Analysis of the QoL impacts of adjuvant chemotherapy found that many domains were adversely affected; however, for most of these domains, QoL returns to baseline levels by 24 months. The adverse impact of adjuvant chemotherapy was significant on most QoL domains at 6 months, including global health status (MD –9.20, 95% CI –11.95 to –6.44; $p < 0.001$), physical functioning (MD –8.05, 95% CI –10.21 to –5.89; $p < 0.001$), role functioning (MD –17.59, 95% CI –21.24 to –13.95; $p < 0.001$), cognitive functioning (MD –5.55, 95% CI –7.97 to –3.13; $p < 0.001$) and social functioning (MD –18.72, 95% CI –22.17 to –15.27; $p < 0.001$).

Mixed-methods research to develop a decision support intervention

An iterative process was used to develop two DESIs (comprising a brief decision aid, a booklet and an online tool) specifically for older women selecting treatment choices, using several evidence sources (the published literature, patient interviews and expert opinion). The DESIs were designed to aid the treatment choice between S+ET or ET ALONE, or, for women who had already received surgery, the decision of whether or not to undergo adjuvant chemotherapy. The online tool component of the DESI was based on models developed using registry data from 23,842 patients and validated on an external data set of 14,526 patients. The 2- and 5-year mortality rates differed by < 1% between predicted and observed values. The models have been embedded in the online tool. Feedback from piloting of the DESI components was excellent and the DESI components were used as the DESI in a cluster-randomised trial to assess whether or not they enhanced shared decision-making in older women.

Cluster-randomised clinical trial of decision support tools

Forty-six UK breast units were randomised (intervention, $n = 21$; usual care, $n = 25$), recruiting 1339 women (intervention, $n = 670$; usual care, $n = 669$). There was no significant difference in global QoL at 6 months post baseline between women in the intervention and usual-care arms (difference –0.20, 95% CI –2.7 to 2.3; $p = 0.90$). In women offered a choice of ET ALONE or S+ET, knowledge about treatments was greater in the intervention arm than in the usual-care arm (94% vs. 74%, respectively; $p = 0.003$). The intervention was associated with significant changes in selection for both S+ET versus ET ALONE, and adjuvant chemotherapy versus no chemotherapy treatments (ET ALONE: rate 21% intervention sites vs. 15% usual-care sites; difference 5.5%, 95% CI 1.1% to 10.0%; $p = 0.02$; adjuvant chemotherapy: rate 10% intervention sites vs. 15% usual-care sites; difference 4.5%, 95% CI 0.0% to 8.0%; $p = 0.013$). Survival was similar in both arms. A process evaluation ran alongside the trial and identified some challenges to DESI implementation, for example a lack of information technology capacity in clinics to allow use of the online tool during patient consultations, but feedback from patients and clinicians was excellent.

Health economic analysis

A probabilistic economic model was developed using registry and cohort study data. For the majority of health and fitness strata, surgery had lower costs and returned more QALYs than ET ALONE. However, for some women aged > 90 years, surgery was no longer cost-effective and generated fewer QALYs than ET ALONE. The incremental benefit of surgery reduced with age and comorbidities. Using the standard NHS cost-effectiveness threshold of £20,000 per QALY, the probability of surgery being cost-effective ranged from 94% for a fit 70-year-old to only 24% for an unfit 90-year-old.

Variation in practice

Analysis of rates of surgery or ET ALONE in UK registry data collected between 2002 and 2010 found that significant numbers of breast units had rates of surgery that were higher or lower than expected. This effect persisted following case mix adjustment for patient age, health status and tumour stage. This analysis was then repeated on the data from the 56 breast units that recruited to the Age Gap cohort study, which confirmed these findings. A mixed-methods exploration of the causes of this variation, including health-care professional interviews and a questionnaire survey that included a discrete choice experiment, found that clinician preferences for S+ET or ET ALONE vary substantially, and decision-making is influenced by patient age, health status, tumour biology and cognitive impairment.

Strengths and limitations of the programme

To the best of our knowledge, this study is the largest analysis to date of outomes in older women with early-stage breast cancer and provides fitness-stratified guidance on treatment and a validated online tool that may be useful in clinical practice to help optimise treatment choice and shared decision-making. Limitations of the Age Gap study relate to recruitment and retention bias identified in the cohort, with a larger proportion of relatively younger women than of older women consenting and remaining with the study for the whole 2-year follow-up period. Limitations for the model used to derive outputs for the Age Gap online tool relate to the lack of data on frailty, which had to be factored in using external data sources (published data), and missing data, which were dealt with using multiple imputation. Limitations of the cluster-randomised trial, for which the primary outcome was QoL, relate to the fact that some women elected not to complete the QoL questionnaires (which were optional) and the very wide variation in baseline scores, especially in women treated with ET ALONE. This made statistical analysis challenging.

Conclusions

The Age Gap programme of research has rigorously developed a robust, evidence-based, age-, health- and tumour-stage-stratified online decision support tool to support shared decision-making for older women faced with two key choices relating to their breast cancer treatment: whether they should undergo S+ET or ET ALONE, or, following surgery, whether or not they should undergo adjuvant chemotherapy. The decision support tools received excellent feedback during piloting and have been subjected to a cluster-randomised clinical trial that demonstrated that they enhance shared decision-making and influence treatment choice. The tool is now available for use on the internet following Medicines and Healthcare products Regulatory Agency (MHRA) approval in 2019. It is hoped that the tool will be widely used in the UK to help reduce the high level of variation in rates of both ET ALONE and adjuvant chemotherapy to ensure that women are neither overtreated nor undertreated, and that they are offered all the evidence they require to make an informed decision that suits their personal preferences.

The data derived from the Age Gap observational cohort study have enabled us to determine thresholds at which surgery and adjuvant chemotherapy cease to have any beneficial effect for older women. This threshold for ET ALONE use is age > 85–90 years in women with significant comorbidity who have ER+ cancers. For adjuvant chemotherapy use, benefit is seen in women age < 80 years if they have high-recurrence-risk ER– or HER-2+ tumours. For those aged > 80 years, there was insufficient evidence to draw any conclusions. The first health economic analysis comparing ET ALONE and S+ET was performed, which similarly confirmed that S+ET is cost-effective for older women up to age 90 years with ER+ breast cancer, based on UK willingness-to-pay thresholds of £20,000 per QALY.

Recommendations for research

The online algorithm is now available (URL: https://agegap.shef.ac.uk/). There are plans to calculate 10-year survival outcomes once data become available in 2025. Application to the UK Cancer Registry will be made at that time and the survival outcomes for the adjuvant chemotherapy versus no chemotherapy and ET ALONE versus S+ET analyses will be re-run, as will the survival analysis for the cluster-randomised controlled trial. In addition, in view of the high value that older women place on QoL and retention of their independence, we plan to modify the Age Gap online tool to provide QoL, adverse event and physcal-function outcomes, alongside the more traditional survival outcomes.

Trial registration

This trial is registered as ISRCTN46099296.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research programme and will be published in full in *Programme Grants for Applied Research*; Vol. 10, No. 6. See the NIHR Journals Library website for further project information.

Programme Grants for Applied Research

ISSN 2050-4322 (Print)

ISSN 2050-4330 (Online)

Programme Grants for Applied Research (PGfAR) was launched in 2013 and is indexed by Europe PMC, NCBI Bookshelf, DOAJ, Ulrichsweb and SCOPUS.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by PGfAR as project number RP-PG-1209-10071. The contractual start date was in July 2012. The final report began editorial review in February 2021 and was accepted for publication in February 2022. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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