The Bridging The Age Gap Study: Determination of optimal therapies for older women with operable breast cancer using retrospective registry data

Paul Richards*[1], Sue Ward[1], Jenna Morgan[1], Catherine Lagord[2], Gill Lawrence[2], Matthew Francis[2], Christopher Lawrence[2], Sarah Lawton[3], Ruth Burns[3], Stephen Walters[1], Karen Collins[4], Malcolm Reed[1], Lynda Wyld[1]

[1]The University of Sheffield, [2]West Midlands Cancer Intelligence Unit, [3]Northern and Yorkshire Cancer Registry and Information Service, [4]Sheffield Hallam University

Background

In the UK, 33% of new breast cancers (BC) are diagnosed in women aged 70 or over, and this is increasing due to improved life expectancy. Approximately 40% of these women do not receive surgery for their breast cancer, despite very low risk of mortality and low risk of serious morbidity. Primary endocrine therapy (PET) is usually offered as an alternative to women with ER+ disease. Similarly older women who would be expected to benefit from adjuvant chemotherapy (i.e. ER- disease, high risk of recurrence) are much less likely to receive it than their younger counterparts.

Trials comparing PET with surgery with and without adjuvant endocrine therapy as treatment for older women with early operable breast cancer were conducted in the 1980s. A review of these trials showed that at the population level PET was as effective as surgery in terms of overall survival, but not disease control [1]. However, these trials took no account of underlying health status or frailty, and did not all select by ER status.

Under-treatment of older women will increase their risk of dying from their breast cancer, and of requiring avoidable additional treatments at a later date. However, due to age-related frailty, co-morbidity and limited life-expectancy, less aggressive treatment may be appropriate for some women. The current evidence base is insufficient to inform decision making for individual women.

The Bridging the Age Gap Study - Overview

One of the central aims of our project is to build a predictive model which can provide estimates for survival and time to treatment failure or recurrence, on the basis of an individual's disease characteristics, age-related health status and proposed treatments. This model will be of benefit to clinicians when discussing appropriate treatment approaches for individual patients.

Other workstreams in the project aim to investigate the extent to which existing treatment decisions vary at a geographical and clinician level, and to study the views of older women about their cancer treatment. These workstreams will combine to create a decision support tool for clinicians and their older breast cancer patients.

Predictive Modelling of Breast Cancer Outcomes

A prospective multi-centre cohort study is being undertaken to provide long-term follow up data to use in this predictive model. This will have detailed information on frailty, quality of life and co-morbidities. However, this will take time to mature. In the meantime routinely collected data from cancer registries will be used as a source of long term follow-up data to build a first iteration of this model. In the future this will be updated with the cohort study data (see Fig 1). Registry data has been used to build other prognostic tools in breast cancer, for example the PREDICT model [2].

Detailed information on underlying health status is not available from cancer registries. However, the linked NHS Hospital Episode Statistics (HES) inpatient dataset will be used to construct a proxy measure of underlying co-morbidities, by looking at reasons for hospital admissions recorded in HES. Overall co-morbidity burden will be measured using the aggregated Charlson Co-morbidity Index, which has been shown to have prognostic ability in breast cancer. Researchers in other cancer areas have used this methodology with HES linked data [3]. Conditions not resulting in hospital admission will not be recorded, so this proxy measure will underestimate the true level of underlying co-morbidity.

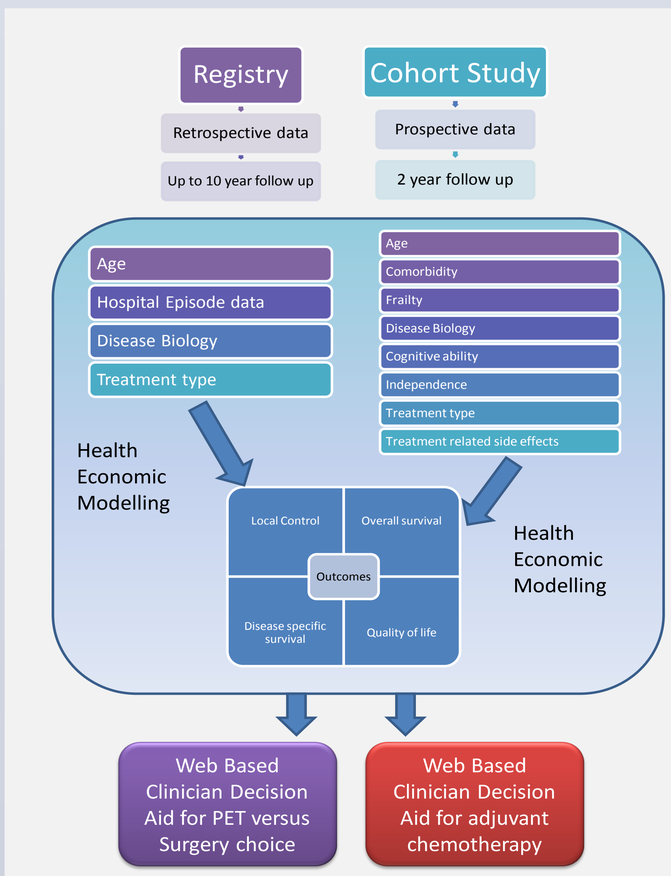


Figure 1. Schematic of the plan for predictive modelling

The retrospective data will allow a first iteration of the predictive model to be built. Whilst survival data and most relevant disease characteristics are available in this data, detailed information on disease control and recurrences, quality of life, and age-related health status will be provided by the cohort study.

These models will be used to build web-based clinical decision aids for treatment planning, as well as health economic evaluation models of different treatment strategies for this population.

The Retrospective Cancer Registry Dataset

Access to HES linked cancer registry records for all women diagnosed with breast cancer aged 70+ from 2002-2010 was agreed with two cancer registries – West Midlands Cancer Intelligence Unit (WMCIU) and Northern and Yorkshire Cancer Registry and Information Service (NYCRIS). The resulting dataset contains 23,960 patients with coverage of ~25% of the UK population.

The distribution of age at diagnosis is presented in Figure 2. The prevalence of co-morbidity for patients diagnosed in the West Midlands region by age is shown in Figure 3. The majority of patients in all age groups have proxy Charlson score of 0. These low reported levels correspond with results from previous studies which measure co-morbidity using the HES proxy Charlson Index [3].

Figure 2. Distribution of age at diagnosis for patients in the retrospective registry dataset

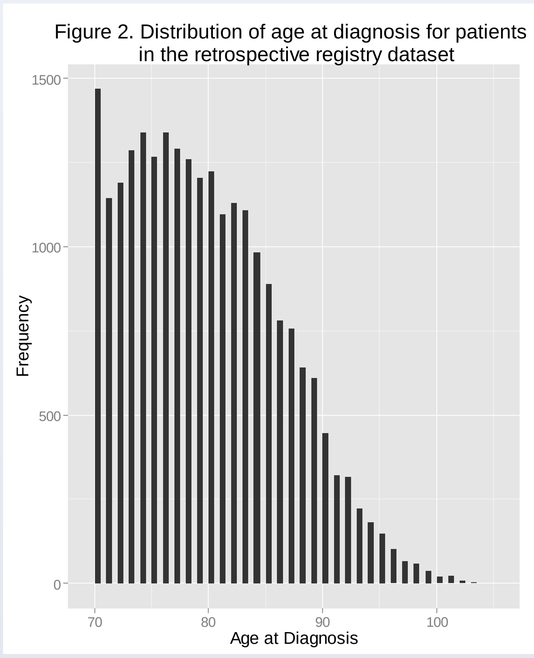
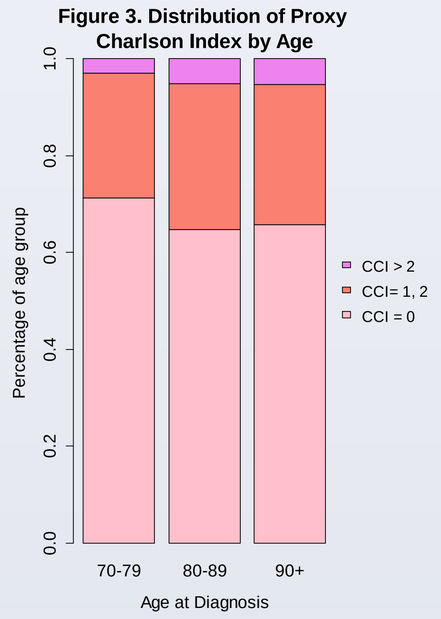


Figure 3. Distribution of Proxy Charlson Index by Age



In order to predict outcomes for women with different disease characteristics receiving different treatments, the cohort is being divided into subgroups for analysis (for example, patients with ER+ve BC by treatment (primary surgery v PET) etc). Problems to be overcome include;

- Incomplete tumour details (ER status, stage at diagnosis etc.)
- Incomplete data on treatments, especially from out-patient settings
- Cannot use "complete case" analysis approach, as ignoring patients with missing data will greatly reduce predictive power and is likely to introduce bias

Algorithms will be developed to define the analysis groups and these will be agreed with the cancer registries. Where there is major uncertainty as to whether or not patients should be included or excluded in a particular subgroup, alternative assumptions will be tested as a sensitivity analysis.

Future Analysis

Once the treatment groups have been defined, parametric survival modeling will be used to predict time-to-event outcomes. Cross-validation methods will be used to test the prognostic ability of the model on a subset of the data not used in the fitting process, and eventually the model will be validated using external data.

The retrospective data is observational in nature with non-random missing values, so apparent treatment effects may be due to the effects of observed or unobserved confounding factors. Where possible, the research team will adopt a Bayesian approach to modeling. Findings from other studies will be used as prior evidence to mitigate against these limitations. This also provides a coherent framework for integrating the cohort data into the initial model once this becomes available.

The development of this methodology will hopefully help other researchers optimise the use of routinely collected cancer registry data to aid decision making.

References and Acknowledgements

1. Hind D, Wyld L, Beverley C, Reed MW. **Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus)**. *Cochrane Database of Systematic Reviews* 2006, Issue 1.
2. Wishart GC, Azzato EM, Greenberg DC, Rashbass J, Kearins O, Lawrence G, Caldas C, Pharoah PDP. **PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer** *Breast Cancer Res. 2010*; 12(1): R1
3. Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, Rachet B, Forman D. **Thirty-day postoperative mortality after colorectal cancer surgery in England** *Gut* 2011; 60:806-813

PR produced the poster text and summary statistics. LW produced Figure 1 detailing the plan for this project. Many thanks go to all members of cancer registry staff who helped in the preparation of the dataset. This publication presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-12098-10071). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

* Corresponding author (p.richards@sheffield.ac.uk)