173P - A deep learning model to predict competing cancer and cardiac risks after anthracycline exposure for early breast cancer

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Introduction

Clinical trials have demonstrated that anthracycline chemotherapy for the adjuvant treatment of early breast cancer (EBC) reduces breast cancer mortality but increases cardiac risk. Attempts to quantify this risk in routine care have been limited by short follow up and inability to adjust for confounding factors and competing risks. The aim of this study was to implement a deep learning framework to quantify excess cardiac risk from anthracycline chemotherapy in real-world care.

Patients treated surgically for stage I-III invasive breast cancer between 2000 & 2016 were identified from in the Scottish Cancer Registry. Information on treatment and clinical outcomes was captured by linkage to the Scottish Morbidity Record and a regional audit database. 4080 EBC patients were identified: 1658 received anthracycline-based chemotherapy (anthra), 297 received non-anthracycline chemotherapy (notanthra) & 2125 received no chemotherapy (chemo).

The primary outcome was a composite of cardiac diagnosis or cardiac death (Cardiac), with competing risks of death from breast cancer (BrC) and death from other causes (Other). At a median follow up of 8.2 years, 448 cardiac events & 559 breast cancer deaths occurred.

Conflict of Interest:
The authors declare that they have no conflict of interest.

Deep Learning Framework

A deep learning framework was constructed to predict patient survival probabilities and competing risk types at discrete time points, given pseudo survival probabilities for each competing risk and patient features including: age, deprivation (SIMD), co-morbidity (Charlson), year of diagnosis, side of radiotherapy, cancer stage & grade, ER & HER 2 status.

After hyper-parameter tuning, the deep learning model predicted cardiac events at 8 years with high confidence (F1-score=0.89), and survival probabilities comparable to the more traditional Fine & Gray model; C-index 0.66, [95% CI 0.62, 0.70] vs. 0.65, [95% CI 0.61- 0.69]).
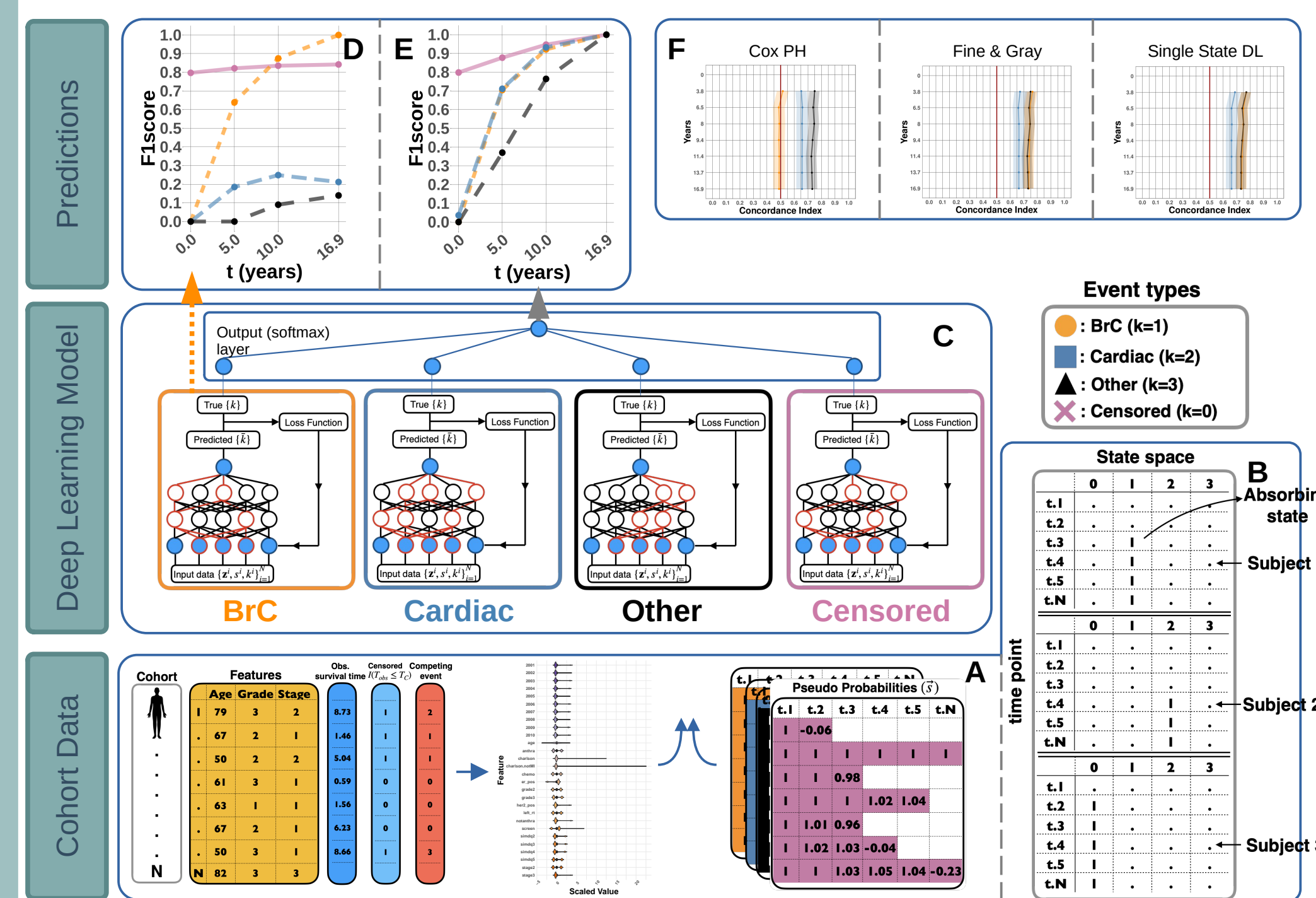

Figure 1: Input data into deep learning model includes patient scaled base-line features, pseudo survival probabilities (A) and state space information (B) at discrete time points. Input data is fed into deep learning model which can operate as a SingleState, or MultiState model with the inclusion of softmax outlayer (C): the deep learning framework was constructed from the Phython Tensorflow and R Keras packages. Accuracy of state space predictions for each competing risk events from Single State (D) and MultiState (E) models at each time point using F1-score. Accuracy of patient survival probabilities at discrete times using Cox-PH, Fine & Gray and SingleState model using Concordance-index (F).

Feature Importance

We perform a permutation analysis to discover feature importance for each competing risk event type, using the trained multistate deep learning model. When a single feature is randomly shuffled in the test data, leaving the target and all other features unperturbed, it will effect the final competing risk event prediction.
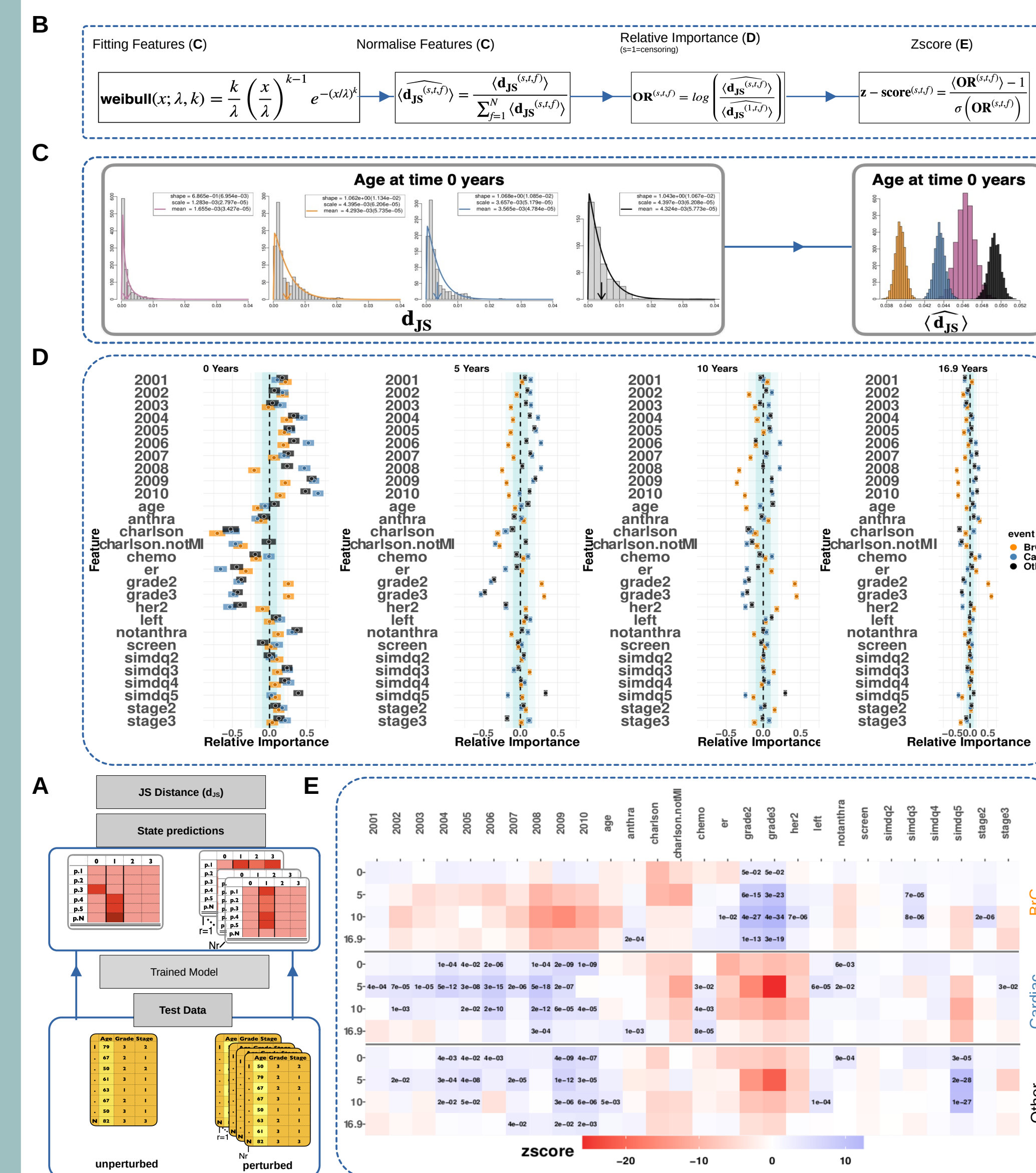

Figure 2: (A) Input data randomly split into training (75%) & test (25%) sets. The MultiState model is first trained fixing the feature relationships found for the test stage. Each feature – at each time point & event type, is tested using the trained model by comparing its unperturbed to perturbed state predictions using the Jenson-Shannon distance (d_{JS}); 5000 perturbations are performed. Each features d_{JS} is fitted using weibull distribution & normalised, relative to the other features at that time point & event type (C). Each features importance – at each time point & each event type, is plotted relative to non-event types (D). Each features corresponding z-scores is plotted & adjusted p.values highlighted (E).

The more important a feature is, the higher the measurement error between the perturbed and unperturbed state predictions. This is because corrupting the structure of the data, by randomly shuffling a feature values, removes any strong relationships our model has learned.

Discussion

Relative to patients whom do not experience any events, the importance of anthracycline exposure (anthra) was not found significant in patients experiencing BrC or Cardiac competing event types until the end of the study – 16 years on. Ineed, for patients experiencing Cardiac event types it was found more important early on whether they received chemotherapy other than anthracycline (notanthra):

	0	5	10	16.9
anthra	-0.16 [-0.2,-0.1]	0.01 [-0.02,0.05]	0.01 [-0.02,0.04]	0.23 [0.18,0.28]
notanthra	0.3 [0.23,0.38]	0.1 [0.07,0.13]	0.04 [0.01,0.07]	0.01 [-0.04,0.07]

Table 1: Odds Ratio (OR) and 95% CI of anthracycline & non-anthracycline chemotherapy exposure for patients experiencing Cardiac event types at discrete time points (years).

High social deprivation status (simdq5) was found important for patients experiencing Other competing risk types, while Grade (grade2 & grade3) remained the most important feature for patients experiencing BrC event types through the duration of the study.

Real world evidence appears reassuring for women treated with anthracyclines for EBC.