

# THE INCIDENCE AND COSTS OF CHEMOTHERAPY SIDE EFFECTS

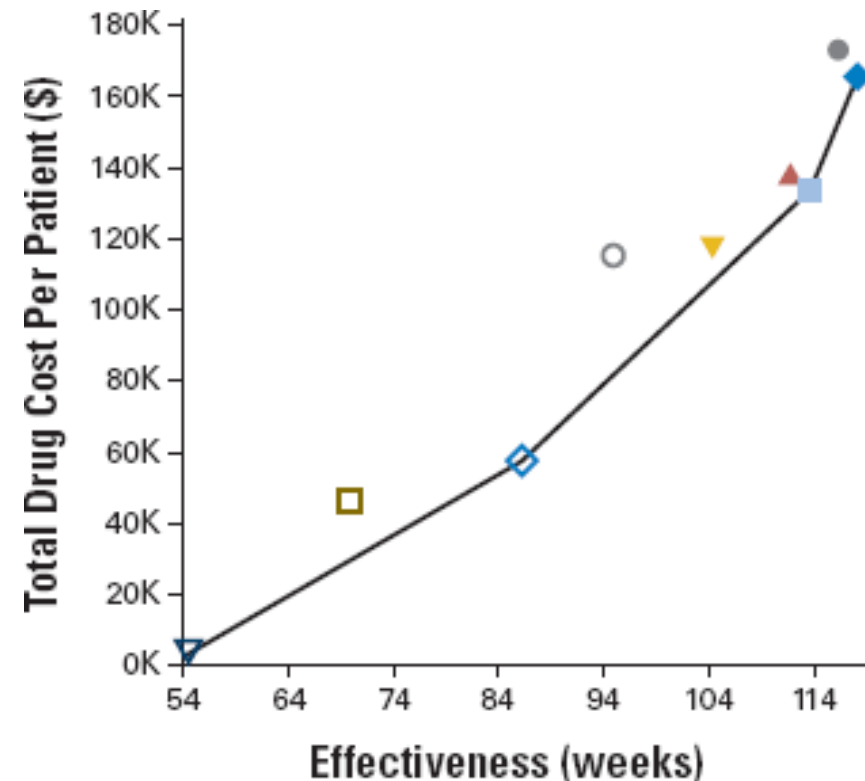
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# Chemotherapy

- Chemotherapy drugs can be life extending for people with cancer. But...
  - ▣ they contribute a small amount to survival
  - ▣ they are increasingly expensive
  - ▣ they cause side effects



# Chemotherapy side effects

- Chemotherapy side effects can:
  - ▣ Impact on patients physical wellbeing
  - ▣ Impact on patients quality of life (QoL)
  - ▣ Potentially impact on cancer survival
  - ▣ Be expensive to manage



# Economic evaluation

- In Australia, new drugs are listed for public subsidy by PBAC on the basis of economic evaluation
- Literature review examined how side effects are incorporated into economic evaluations of chemotherapy
  - ▣ Costs and outcomes of side effects are not included in any systematic way
  - ▣ Clinical trials are the primary source of probabilities
  - ▣ Resource use is often estimated with expert opinion or based on best practice
- These data sources may not reflect clinical practice
- If side effects aren't accounted for (accurately) then outcomes of economic evaluations may be biased

# Aims & Objective

- Overall objective:
  - ▣ To better inform models of chemotherapy cost effectiveness
- Aims:
  - ▣ Explore in clinical practice:
    1. the incidence of chemotherapy side effects
    2. the factors which influence the incidence of chemotherapy side effects
    3. the resource use associated with chemotherapy side effects

# Department of Veterans Affairs

- The Australian Government Department of Veterans Affairs provides services to nearly 500,000 war veterans and their families in Australia
- Clients with a 'gold card' are entitled to the full range of services at DVA's expense
- DVA has actively encouraged the use of their data to undertake pharmacoepidemiological research

# Data linkage

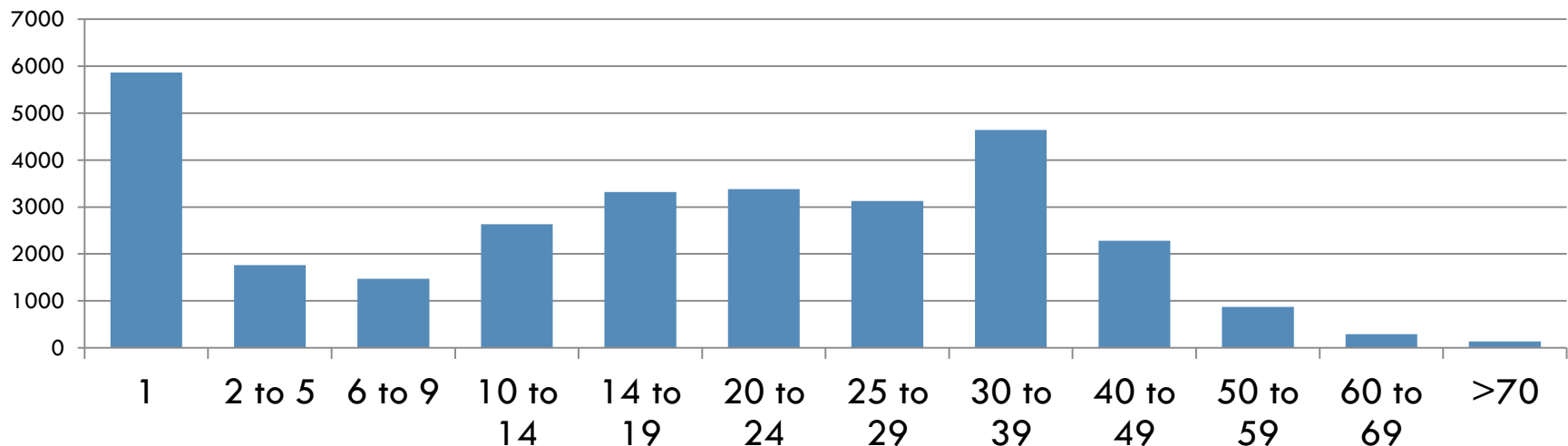
- Extract from DVA client database – individuals residing in NSW 1994 – 2007
- Linked by CHeReL to NSW population data

| Registry                           | Start Date         | End Date            |
|------------------------------------|--------------------|---------------------|
| NSW Cancer Registry                | Jan 1994           | Dec 2009            |
| Repatriation PBS                   | 01 July 2004       | 31 Jan 2010         |
| Repatriation MBS                   | 01 Jan 2000        | 31 Jan 2010         |
| Admitted Patient Data Collection   | 01 July 2000       | 30 June 2009        |
| Emergency Department Data          | 01 Jan 2005        | 31 Dec 2009         |
| <b>Resource utilisation period</b> | <b>01 Jan 2005</b> | <b>30 June 2009</b> |

# Sample

|   |          |
|---|----------|
| □ Individual Gold Card Holders          | 1 29,307 |
| □ Individuals with a cancer diagnosis   | 29,480   |
| □ Individuals who received chemotherapy | 12,030   |
| □ Total doses of chemotherapy           | 1 11,059 |

**No. of PBS products per person with cancer**





# Demographics

| Demographic                                 | Chemo cohort |
|---|--------------|
| Proportion males                            | 72%          |
| Mean age (median) in years                  | 81 (83)      |
| age range                                   | 46 - 106     |
| age group <70 yrs                           | 14%          |
| 70-80 yrs                                   | 23%          |
| >80 yrs                                     | 63%          |
| Mean Rx Risk score (weighted comorbidities) | 8.83         |
| RxRisk score range                          | 0 - 26       |

# Cancer

| Cancer site                | N    | % of cancer |
|----------------------------|------|-------------|
| Prostate                   | 3124 | 39.17       |
| Breast                     | 1059 | 13.28       |
| Melanoma of skin           | 881  | 11.05       |
| Colon                      | 491  | 6.16        |
| Lung                       | 354  | 4.44        |
| Non-Hodgkin's lymphoma     | 349  | 4.38        |
| Rectum, rectosigmoid, anus | 279  | 3.5         |
| Bladder                    | 186  | 2.33        |
| Ill-def & unspec site      | 136  | 1.71        |
| Head & neck                | 591  | 0.65        |

# Chemotherapy

| Drug                | Frequency | % of chemo | Used to treat...                |
|---------------------|-----------|------------|---------------------------------|
| Fluorouracil        | 2198      | 18.20      | Breast, colorectal              |
| Goserelin acetate   | 1909      | 15.80      | Prostate, breast                |
| Leuprorelin acetate | 1307      | 10.82      | Prostate                        |
| Bicalutamide        | 1005      | 8.32       | Prostate, breast                |
| Tamoxifen citrate   | 776       | 6.42       | Breast                          |
| Capecitabine        | 327       | 2.71       | Breast, colorectal              |
| Rituximab           | 321       | 2.66       | Lymphoma                        |
| Cyclophosphamide    | 305       | 2.53       | Breast, leukemia                |
| Anastrozole         | 280       | 2.32       | Breast                          |
| Gemcitabine         | 276       | 2.28       | Breast, lung, bladder, pancreas |

# Overview of methods

- 4 common side effects examined:
  - ▣ Diarrhoea, anaemia, nausea and vomiting (N&V), and neutropenia
  
- Aim 1 – incidence of side effects
  - ▣ The incidence of each side effect was calculated
- Aim 2 – factors influencing incidence of side effects
  - ▣ Multiple regression analysis using generalised estimating equations identified factors which influence the incidence of each side effect
- Aim 3 – resource use associated with side effects
  - ▣ Multiple linear regression identified whether those who experienced a side effect had higher chemotherapy costs

# Overview of assumptions

- No direct data on whether someone experiences a side effect, so require a proxy
- Specific treatments are likely (based on best practice) to be given when an individual experiences a side effect
- These treatments can be related to chemotherapy administration by time
- In interpretation, need to consider:
  - ▣ “Individuals treated for a likely side effect”
  - ▣ individuals having these treatments for reasons other than side effects
  - ▣ individuals having side effects and not receiving these treatments
- Treatment of a side effect was considered related to chemotherapy when it occurred on or within three days after a chemotherapy dose

# Incidence of side effects - method

- An analysis dataset was generated for each side effect
- For each dose of chemotherapy dispensed, a search was done of any side effect treatments which were given to the same individual within 3 days
- The incidence was calculated by dose of chemotherapy, and then by individual

# Incidence of side effects - results

|           | Side effects      | No. with chemotherapy | No. with side effect | % with side effect |
|-----------|-------------------|-----------------------|----------------------|--------------------|
| By doses  | Diarrhoea         | 89,594                | 879                  | 1%                 |
|           | Anaemia           | 84,872                | 638                  | <1%                |
|           | Nausea & vomiting | 84,378                | 5,415                | 6%                 |
|           | Neutropenia       | 84,495                | 601                  | <1%                |
| By person | Diarrhoea         | 7,978                 | 396                  | 5%                 |
|           | Anaemia           | 8,158                 | 330                  | 4%                 |
|           | Nausea & vomiting | 9,173                 | 1,535                | 17%                |
|           | Neutropenia       | 8,069                 | 242                  | 3%                 |

# Factors influencing side effects - methods

- Multiple regression used to identify factors which influence the incidence of each side effect
- Binary outcome, so logistic model required
- Correlated data noted
  - Can restructure data to remove correlation, using a summary measure (eg: ever had a side effect), or
  - Can use technique designed for correlated data, such as Generalised Estimating Equations (GEE)



# Generalised estimating equations

- Allow the correlation of outcomes within an individual to be estimated and taken into account in the regression coefficients and their standard errors
- The regression coefficients obtained from GEE are correctly interpreted in a population averaged manner
- Specifications of my GEE models
  - ▣ Repeated subject variable: PPN
  - ▣ Distribution: Binomial
  - ▣ Link function: Logit

# GEE Correlation structures

- Independent – simplest assumption, but usually incorrect
  - ▣ Each observation for an individual is uncorrelated with every other observation for that individual.
  - ▣ The GEE reduces to the independence (GLM) estimating equation
- Exchangeable (compound symmetry)
  - ▣ Every observation within an individual is equally correlated with every other observation from that individual.
  - ▣ Fully characterised by the intraclass correlation coefficient
- Auto-regressive
  - ▣ Derived from time series analysis
  - ▣ Two observations taken close in time within an individual tend to be more highly correlated than two observations taken far apart in time from the same individual.
- Others, inc unstructured and user fixed – more complicated and situation specific

# Factors influencing side effects - methods

*side effect*  $\sim \alpha + \text{gender} + \text{age} + \text{RxRisk} + \text{chemo} + \text{cancer} + \varepsilon$

| Variable                  | Levels  |
|---------------------------|---|
| Side effect               | Yes / No  |
| Gender                    | Male / Female   |
| Age                       | Continuous, or<br><70 years<br>70 – 79 years<br>>79 years |
| RxRisk<br>(comorbidities) | Quartiles (0-7, 8-9, 10-12, 13-26)                        |
| Chemo                     | Consolidated to 8 levels based on ATC code                |
| Cancer                    | Consolidated to 7 levels based on ICD classification      |

# Factors influencing side effects - models

- Tested correlation structures to maximise model fit with all variables at least aggregated level
  - ▣ Autoregressive consistently chosen as most appropriate
  - ▣ Indicates that there is correlation based on time as well as individuals
- Tested models with aggregated variable levels for age (continuous vs 4 levels) and chemotherapy category (2 categorisations each with 8 levels)
  - ▣ Model 1 (continuous age and standard chemo categories) most appropriate for  $\frac{3}{4}$  side effects

# Summary of results

| Variable                      | Diarrhoea   | Nausea & vomiting | Anaemia     | Neutropenia |
|-------------------------------|-------------|-------------------|-------------|-------------|
| Gender (female)               | ND          | Increase***       | ND          | ND          |
| Age (younger)                 | Increase*** | Increase***       | ND          | ND          |
| RxRisk (fewer co-morbidities) | Decrease*   | Decrease*         | Decrease*** | Decrease**  |

\* <0.05, \*\*<0.01, \*\*\*<0.001

- Females are 1.6 times more likely to experience N&V
- Every additional year of age decreases odds of diarrhoea by 4% and decreases odds of N&V by 3%
- Moving from highest to lowest RxRisk reduces odds of a side effect by 25% (N&V) to 60% (neutropenia)

# Summary of results

| Variable          | Diarrhoea | Nausea & vomiting | Anaemia | Neutropenia |
|-------------------|-----------|-------------------|---------|-------------|
| Breast cancer     | ND        | Decrease*         | ND      | Increase*** |
| Colorectal cancer | ND        | ND                | ND      | Increase*** |
| Genital cancer    | ND        | ND                | ND      | Increase*** |
| Lung cancer       | Decrease* | ND                | ND      | Increase*** |
| Non-solid tumours | Decrease* | Decrease***       | ND      | Increase*** |
| Other             | ND        | ND                | ND      | Increase*** |

- Compared to urinary cancer: \* <0.05, \*\*<0.01, \*\*\*<0.001
  - diarrhoea odds were 70% lower in lung and 60% lower in non-solid cancers
  - N&V odds were reduced by nearly half in breast cancer and by over 60% in non-solid tumours
  - The increase of odds of neutropenia was highest for non-solid tumours (50-fold) and lung cancers (20-fold)

# Summary of results

| Variable             | Diarrhoea   | N&V         | Anaemia     | Neutropenia |
|----------------------|-------------|-------------|-------------|-------------|
| Antineoplastic       | Decrease*** | Increase*** | ND          | Increase*   |
| Progestogens         | ND          | Increase*   | ND          | ND          |
| LHRH agnoids         | Decrease*** | Increase*** | Decrease**  | Increase*** |
| Anti-estrogens       | Decrease*   | Increase*** | ND          | Increase*** |
| Anti-androgens       | Decrease**  | Increase*** | Decrease*** | Increase*   |
| Aromatase inhibitors | Decrease*   | ND          | Decrease*   | ND          |
| Immunostimulants     | ND          | ND          | ND          | Increase*** |

\* <0.05, \*\*<0.01, \*\*\*<0.001

## □ Compared to immunosuppressants:

- Antineoplastics lower odds of diarrhoea by over 70%
- Anti-androgens increased odds of N&V by 13-fold
- AIs decrease odds of anaemia by 84%
- Immunostimulants increased odds of neutropenia by 700-fold

# Resource use - methods

*Total cost ~  $\alpha$  + gender + age + RxRisk + cancer + doses + any se +  $\varepsilon$*

| Variable        | Levels  |
|-----------------|---|
| Total cost      | Total health care expenditure (medical services, hospitalisation &/or pharmaceuticals) during the 6-month period following the first dose of a new chemotherapy regimen from 1 <sup>st</sup> Jan 2005 |
| Gender          | Male / Female   |
| Age             | <70 years<br>70 – 79 years<br>>79 years   |
| RxRisk          | Quartiles (0-7, 8-9, 10-12, 13-26)  |
| Doses           | Total number of doses of chemotherapy (continuous)  |
| Cancer          | Consolidated to 7 levels based on ICD classification  |
| Any side effect | Diarrhoea OR Anaemia OR N&V OR Neutropenia  |

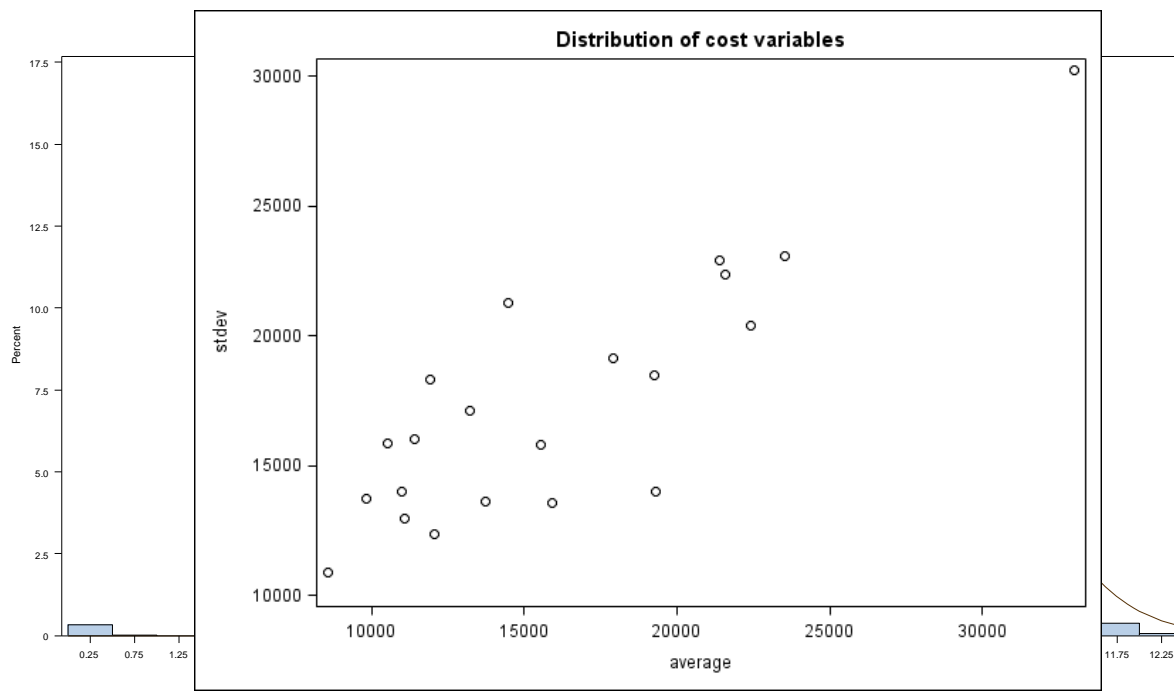


# Resource use- data distribution

- Cost data are typically positively skewed and truncated at zero, making parametric tests difficult
- Options include:
  - ▣ If large sample size, ignore skew (central limit theorem)
  - ▣ Non-parametric tests – inappropriate for decision makers
  - ▣ Transform data – retransformation difficult
  - ▣ Non-parametric bootstrapping – simulation method, but doesn't model the skewness of the data
  - ▣ Generalised linear modelling – allows responses to be distributed in other ways (often gamma distribution is appropriate for cost data)

# Resource use - results

- Data highly skewed
- Log-transformed data approaches normal
- Mean vs standard deviation for raw costs shows an approximate constant coefficient of variation



# Resource use – raw cost results

| Solution for Fixed Effects - Simple linear regression of costs and each AE |           |                 |                |         |
|--|-----------|-----------------|----------------|---------|
| Effect   | Category  | Estimate        | Standard Error | Pr >  t |
| Intercept  |           | 39705           | 3131.98        | <.0001  |
| Sex (vs male)  | Female    | -1418.69        | 599            | 0.0179  |
| age  |           | <b>-140.26</b>  | 30.3976        | <.0001  |
| RxRisk   |           | <b>552.77</b>   | 59.6786        | <.0001  |
| Cancer site<br>(vs urinary)  | Breast    | <b>-4148.06</b> | 1299.15        | 0.0014  |
|  | CRC       | 616.02          | 1206.16        | 0.6096  |
|  | Genital   | <b>-3231.73</b> | 1097.67        | 0.0033  |
|  | Lung      | 237.14          | 1395.47        | 0.8651  |
|  | Non-solid | <b>4655.44</b>  | 1214.67        | 0.0001  |
|  | Other     | -2693.62        | 1150.71        | 0.0193  |
| Any diarrhoea  | No        | <b>2498.68</b>  | 977.5          | 0.0106  |
| Any nausea/vomit   | No        | <b>-7511.1</b>  | 543.34         | <.0001  |
| Any anaemia  | No        | <b>-4724.43</b> | 1042.62        | <.0001  |
| Any neutropenia  | No        | <b>-10631</b>   | 1141.47        | <.0001  |

# Resource use – log-transformed results

| Solution for Fixed Effects - Regression of log costs – each AE |           |                |                |         |
|--|-----------|----------------|----------------|---------|
| Effect   | Category  | Estimate       | Standard Error | Pr >  t |
| Intercept  |           | 10.2124        | 0.2335         | <.0001  |
| Sex (vs male)  | Female    | <b>-0.2062</b> | 0.04466        | <.0001  |
| age  |           | -0.00565       | 0.002266       | 0.0127  |
| RxRisk   |           | <b>0.06941</b> | 0.004449       | <.0001  |
| Cancer site<br>(vs urinary)                                    | Breast    | <b>-0.3471</b> | 0.09686        | 0.0003  |
|  | CRC       | -0.077         | 0.08992        | 0.3919  |
|  | Genital   | -0.1911        | 0.08184        | 0.0195  |
|  | Lung      | -0.167         | 0.104          | 0.1084  |
|  | Non-solid | <b>0.1749</b>  | 0.09056        | 0.0535  |
|  | Other     | <b>-0.3751</b> | 0.08579        | <.0001  |
| Any diarrhoea  | No        | -0.01491       | 0.07288        | 0.8379  |
| Any nausea/vomit   | No        | <b>-0.5665</b> | 0.04051        | <.0001  |
| Any anaemia  | No        | <b>-0.3472</b> | 0.07773        | <.0001  |
| Any neutropenia  | No        | <b>-0.5458</b> | 0.0851         | <.0001  |

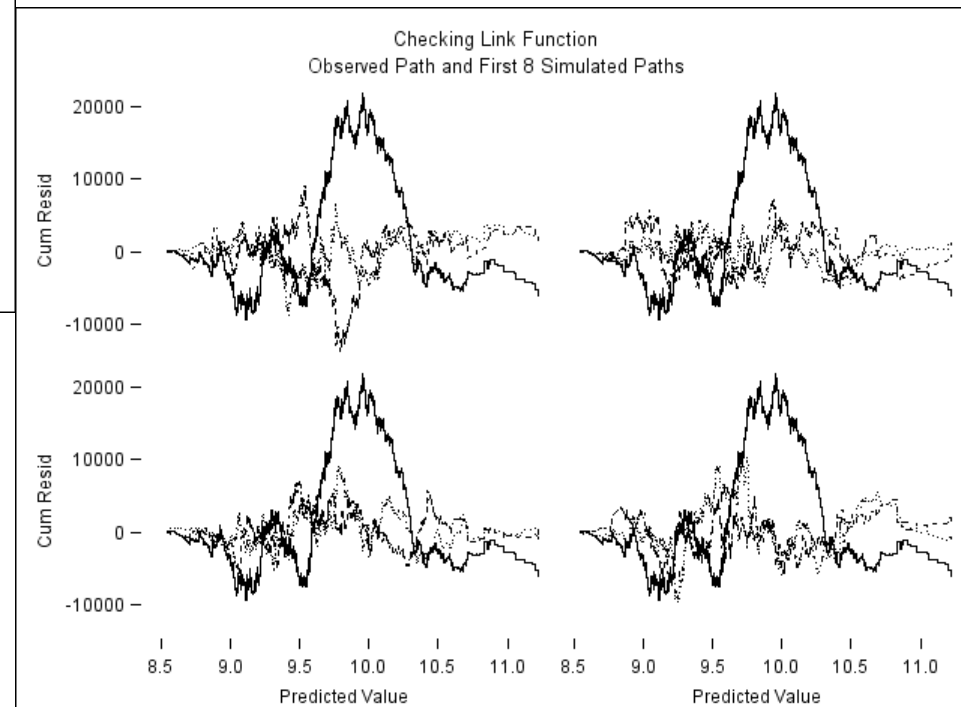
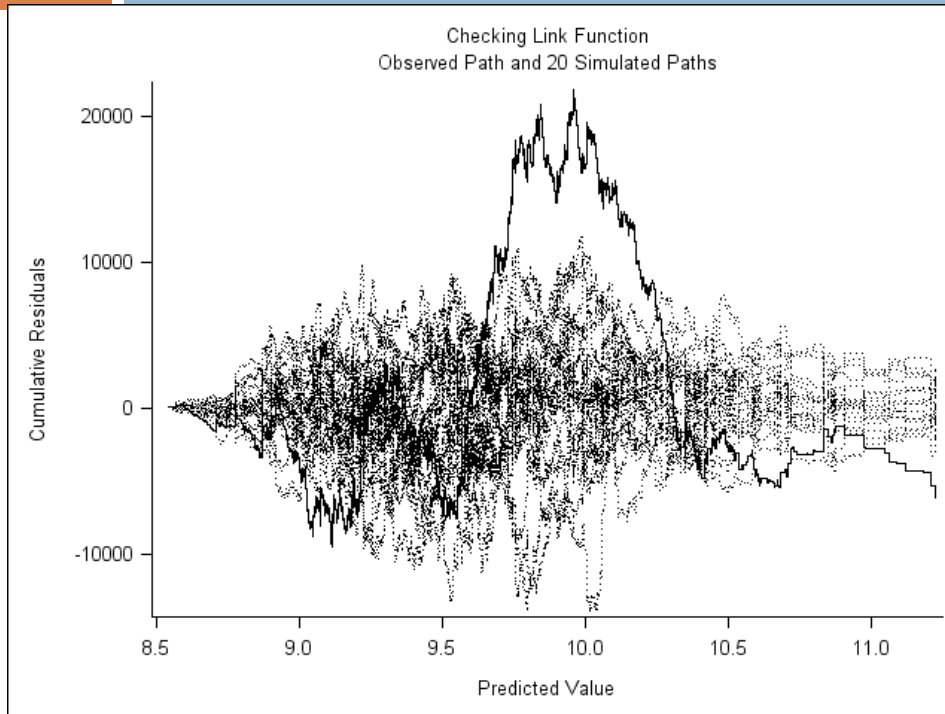
# Resource use – GLM results

| Parameter  | Category | Exp (Estimate) | Exp (Wald 95% Confidence Limits) |          |
|------------|----------|----------------|----------------------------------|----------|
| Intercept  |          | 14237.01       | 10515.44                         | 19273.76 |
| Sex        | F        | 0.91           | 0.84                             | 0.97     |
| age        |          | 0.99           | 0.99                             | 1.00     |
| RxRisk     |          | 1.05           | 1.04                             | 1.06     |
| sitecatb   | Breast   | 0.67           | 0.59                             | 0.75     |
| sitecatb   | Genita   | 0.76           | 0.70                             | 0.83     |
| sitecatb   | Lung     | 1.10           | 0.96                             | 1.25     |
| sitecatb   | Nosoli   | 1.25           | 1.12                             | 1.39     |
| sitecatb   | Other    | 0.76           | 0.69                             | 0.83     |
| sitecatb   | Urinar   | 1.01           | 0.87                             | 1.16     |
| anydia     | 1        | 0.89           | 0.79                             | 1.00     |
| anynausea  | 1        | 1.61           | 1.51                             | 1.72     |
| anyanaemia | 1        | 1.33           | 1.18                             | 1.51     |
| anyneut    | 1        | 1.54           | 1.34                             | 1.76     |
| Scale      |          | 2.95           | 2.85                             | 3.06     |

# Resource use – GLM results

- Test model
  - ▣ Plot cumulative residuals to assess fit of covariates or appropriateness of link function
  - ▣ Assesses if the simulated residual patterns (with a log-link) that would be generated by the model under the specified assumptions are statistically different from the one actually generated

# Resource use – GLM results



# Resource use – GLM results

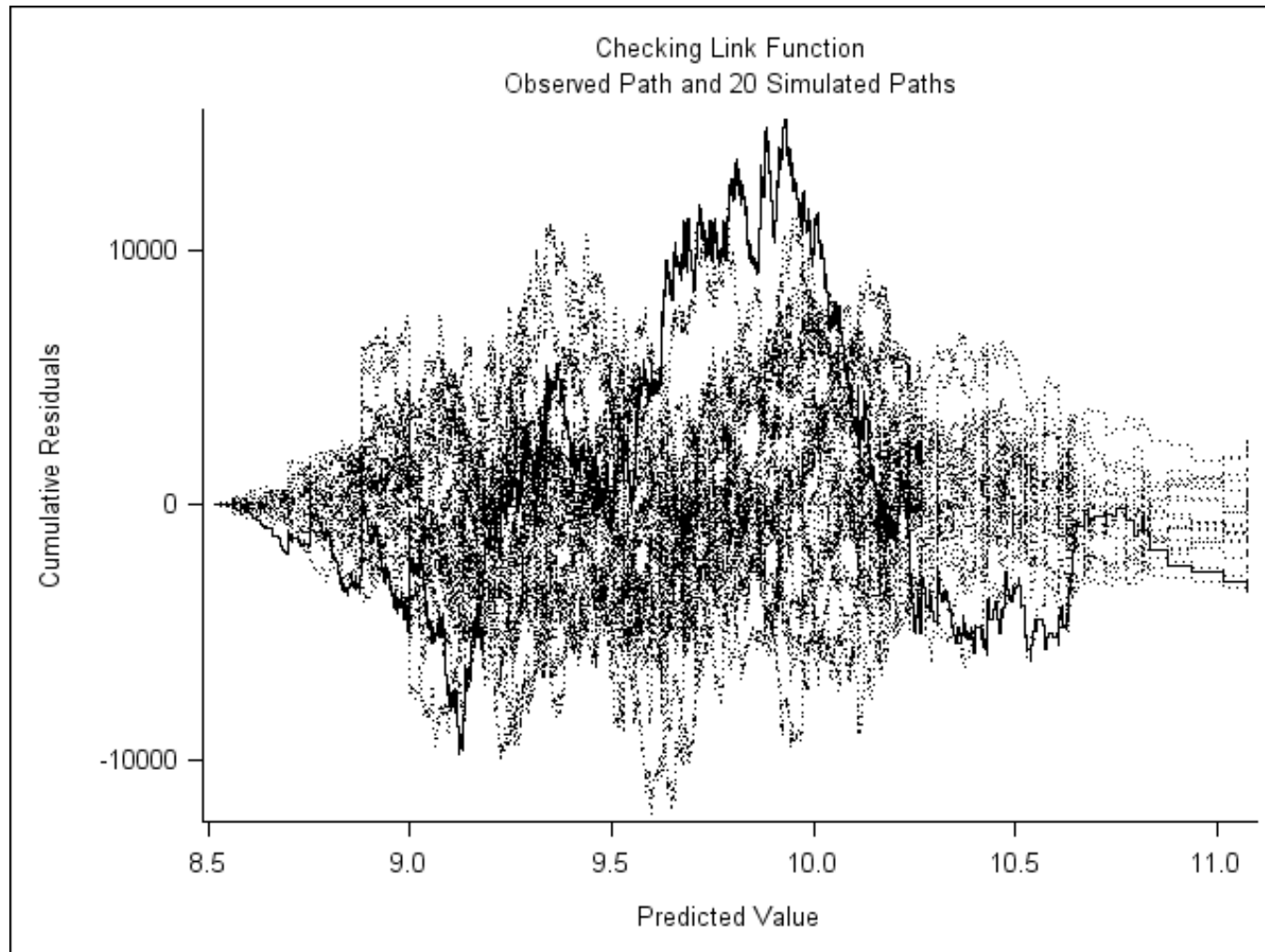
- Plots indicate an artefact in the data
- Exploratory analysis of model with interaction terms
  - ▣ Between side effects
    - 2/3 anaemia interactions were significant at  $p < 0.05$  level
  - ▣ Between the type of cancer and the side effect
    - Nausea had the strongest association with type of cancer
  - ▣ Between age and comorbidities
    - Not significant



# Resource use – GLM results

- Final model included:
  - ▣ Main effects
  - ▣ Interaction term for anaemia and other side effects
  - ▣ Interaction term for nausea and cancer type
- Little impact on the significance of the main effects on total cost
- A number of interaction terms appear to significantly influence total cost
- Inclusion of interaction terms appears to improve model fit

# Resource use – GLM results



# Conclusions

- This large administrative dataset provides an opportunity to examine 'real life' incidence of chemotherapy side effects in older people
- Being treated for a likely side effect is more common in individuals who are older or who have more co-morbidities
- Being treated for a likely side effect may be influenced by the type of cancer and chemotherapy an individual has
- Being treated for a likely side effect significantly increases overall healthcare costs

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