The incidence and costs of chemotherapy side effects

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THE INCIDENCE AND COSTS OF CHEMOTHERAPY SIDE EFFECTS

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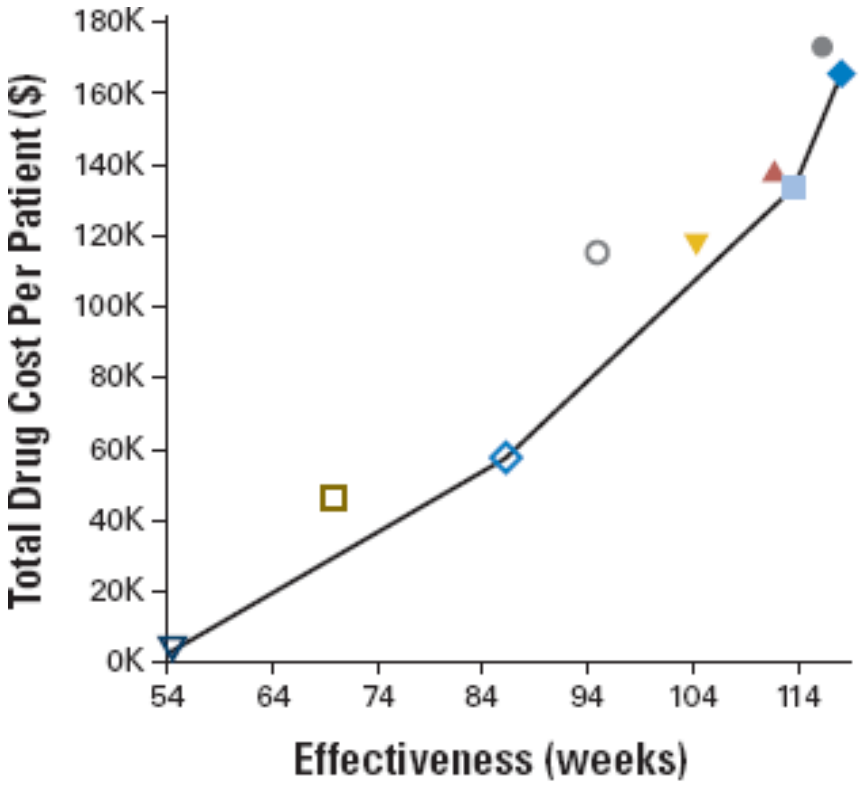
CAER 2013

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

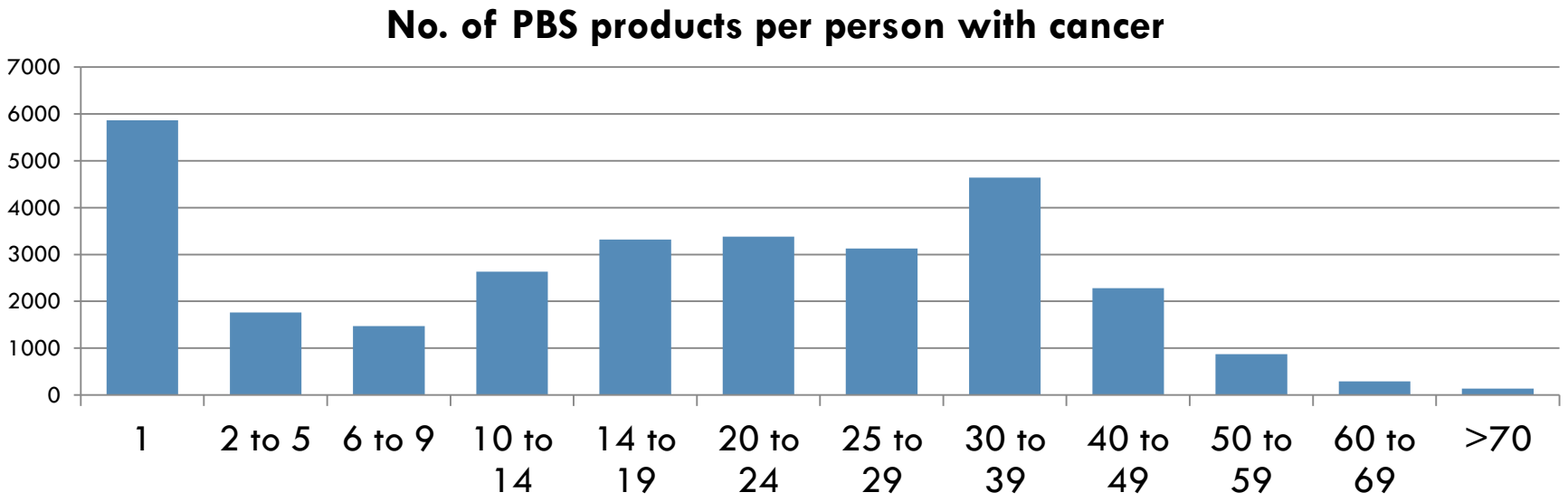
Data linkage

- 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
Resource utilisation period	**01 Jan 2005**	**30 June 2009**

Sample

- Individual Gold Card Holders 129,307
  - Individuals with a cancer diagnosis 29,480
  - Individuals who received chemotherapy 12,030
  - Total doses of chemotherapy 111,059



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
Anastrazole	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 that 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

$$side\ effect \sim \alpha + gender + age + RxRisk + chemo + cancer + \varepsilon$$

Variable	Levels
Side effect	**Yes / No**
Gender	Male / Female
Age	Continuous, or <70 years 70 – 79 years >79 years
RxRisk (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 ¾ 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 are1.6 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***

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

- Compared to urinary cancer:
  - 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 agnoists	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 immunosuppresants:
  - 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

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

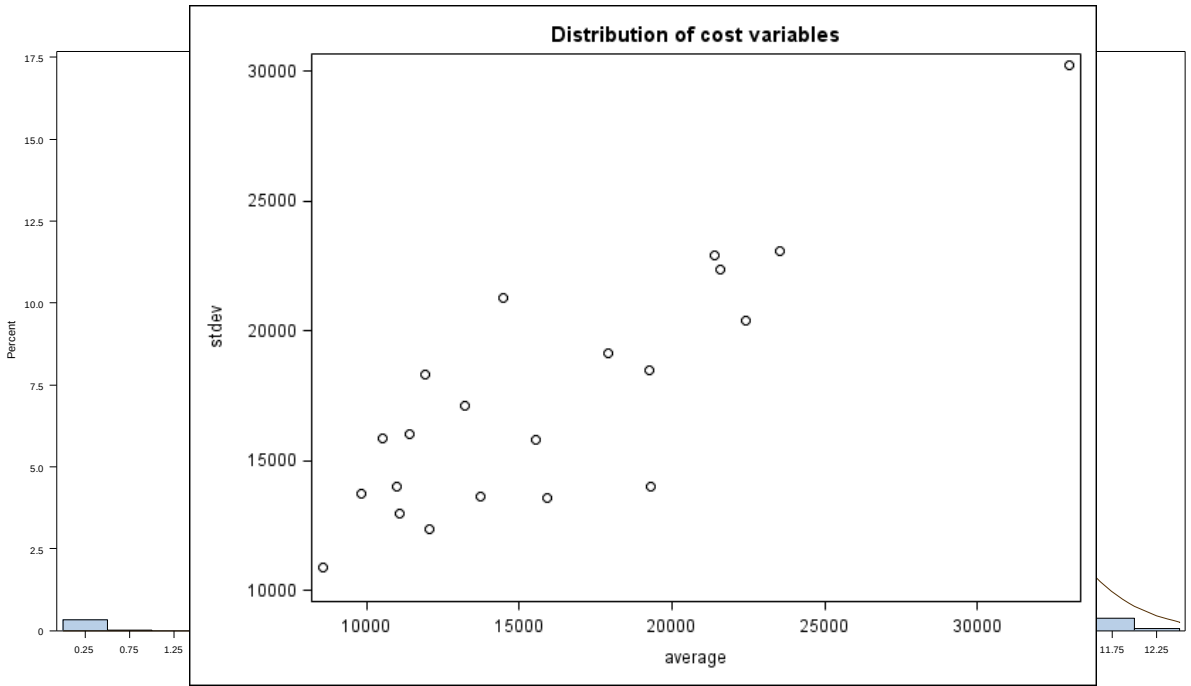
Variable	Levels
Total cost	Total health care expenditure (medical services, hospitalisation &/or pharmaceuticals) during the 6-month period following the first dose of a new chemotherapy regimen from 1st Jan 2005
Gender	Male / Female
Age	<70 years 70 – 79 years >79 years
RxRisk	Quartiles (0-7, 8-9, 10-12, 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-paramatric 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		**-140.26**	30.3976	<.0001
RxRisk		**552.77**	59.6786	<.0001
Cancer site (vs urinary)	**Breast**	**-4148.06**	1299.15	0.0014
	CRC	616.02	1206.16	0.6096
	Genital	**-3231.73**	1097.67	0.0033
	Lung	237.14	1395.47	0.8651
	Non-solid	**4655.44**	1214.67	0.0001
	Other	-2693.62	1150.71	0.0193
Any diarrhoea	**No**	2498.68	977.5	0.0106
Any nausea/vomit	**No**	**-7511.1**	543.34	<.0001
Any anaemia	**No**	**-4724.43**	1042.62	<.0001
Any neutropenia	**No**	**-10631**	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**	**-0.2062**	0.04466	<.0001
age		-0.00565	0.002266	0.0127
RxRisk		**0.06941**	0.004449	<.0001
Cancer site (vs urinary)	**Breast**	**-0.3471**	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	0.1749	0.09056	0.0535
	Other	**-0.3751**	0.08579	<.0001
Any diarrhoea	**No**	-0.01491	0.07288	0.8379
Any nausea/vomit	**No**	**-0.5665**	0.04051	<.0001
Any anaemia	**No**	**-0.3472**	0.07773	<.0001
Any neutropenia	**No**	**-0.5458**	0.0851	<.0001

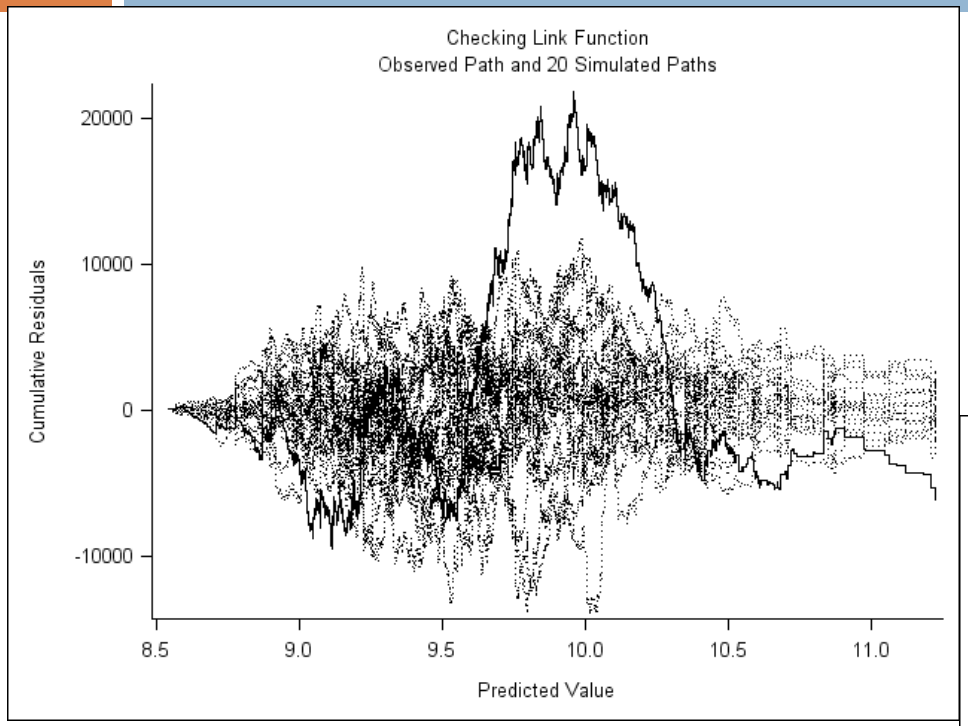
Resource use – GLM results

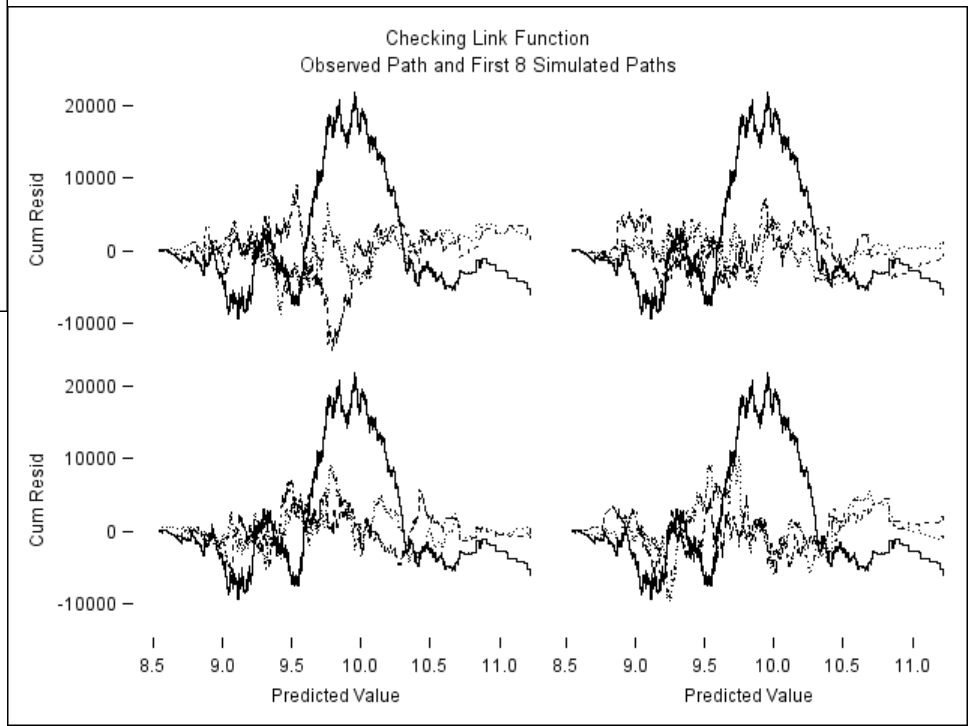
Parameter	Category	Exp (Estimate)	Exp (Wald 95% Confidence Limits)	
Intercept		14237.01	10515.44	19273.76
Sex	F	0.91	0.84	0.97
age		0.99	0.99	1.00
RxRisk		1.05	1.04	1.06
sitecatb	Breast	0.67	0.59	0.75
sitecatb	Genita	0.76	0.70	0.83
sitecatb	Lung	1.10	0.96	1.25
sitecatb	Nosoli	1.25	1.12	1.39
sitecatb	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





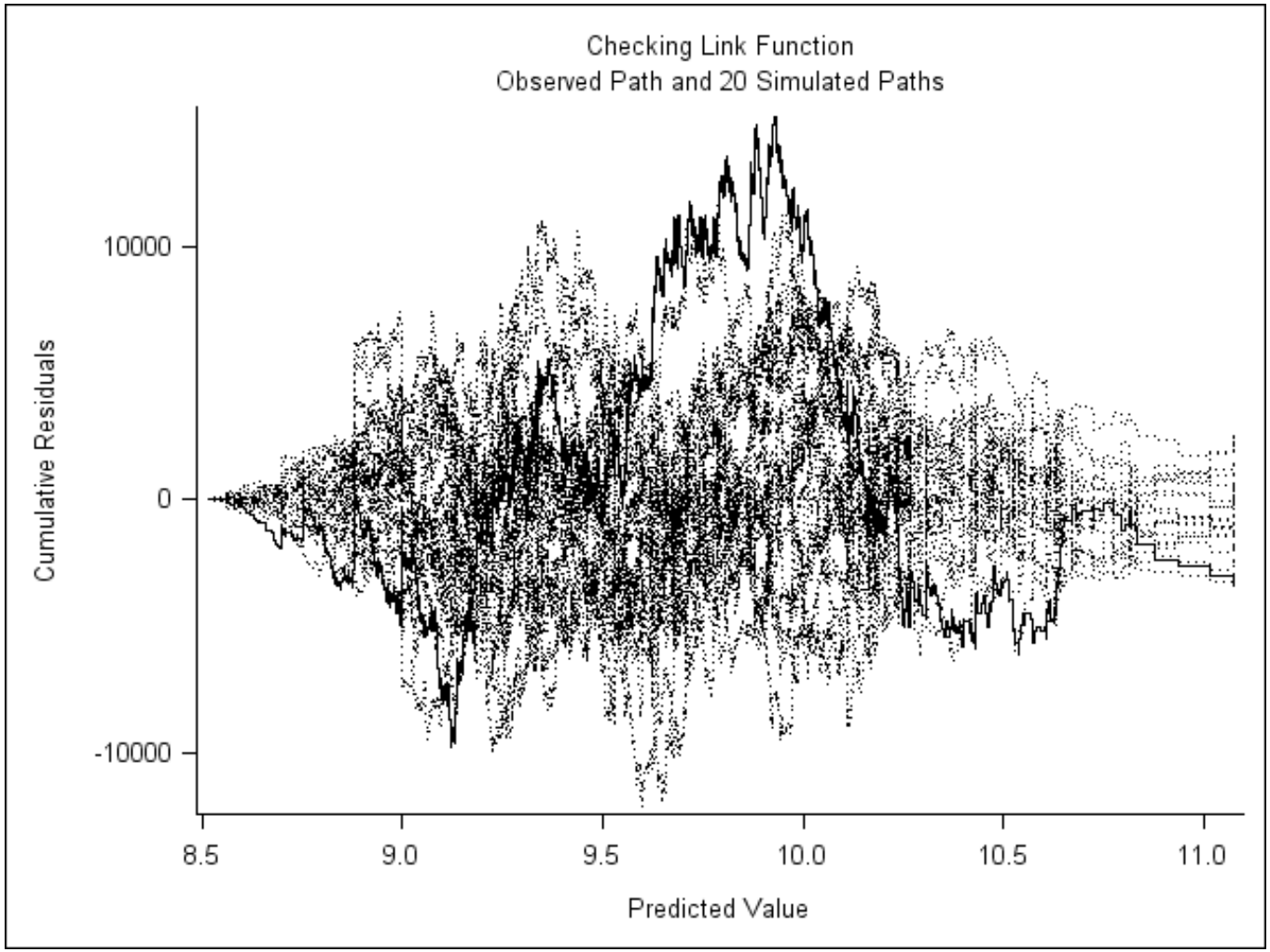
Resource use – GLM results

- 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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