Statistical Inference Under Latent Class Models, With Application To Cancer Survivorship Study

X. Joan Hu

Department of Statistics and Actuarial Science
Simon Fraser University, British Columbia, Canada

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Joint work with Huijing Wang and John Spinelli

Outline

1. Introduction: Large Administrative Health Data

Readily Available

- Canadian Provincial Medical Insurance Databases

- Canada Health Care System: universally accessible, government-sponsored

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- Canadian Disease/Patient Registries: e.g. BC Cancer Registry

1. Introduction: to Address Public Health Issues with Such Data

McBride et al (2010) on Cancer Survivorship

- The cancer survivor population has been increasing rapidly due to improvements in cancer treatments.
- These survivors are often at risk of subsequent and ongoing problems that are mainly treatment related.
- The evaluation/development of strategies for long-term management requires risk assessment, particularly for those diagnosed at a young age, e.g. at age 0 to 19.

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BC Cancer Agency
CARE + RESEARCH

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e.g. **physician claims** of the survivors.

1. Introduction: CAYACS Physician Claims Study

CAYACS Data Extraction

- **CAYACS survivor cohort**: diagnosed 1981-1999, under the age of 20, in BC and having survived $\geq$ 5 yrs
  - information from Cancer Registry (a total of 1962)
  - physician claims from MSP (Medical Services Plan), starting from 5 yrs after diagnosis till 2006

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  - physician claims from MSP (Medical Services Plan), starting from 5 yrs after diagnosis till 2006
- **CAYACS general population sample**: selected from BC general population to match in sex and birth year, 10 times the size of survivor cohort.
  - physician claims from MSP

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  - to evaluate the cohort's physician visit frequency and medical cost
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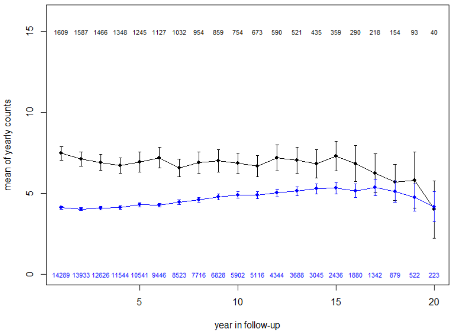
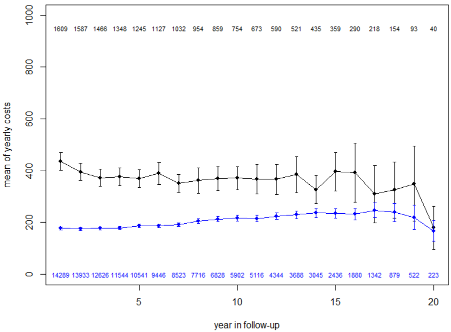
- **Results from CAYACS's previous analysis: 3-year visit counts:** (McBride et al, 2011)
  Regarding medical care demand:
  - cancer survivors > general population
    survivors often suffered the consequences of the original cancer diagnoses – mostly treatment-related (later effects)
  - females > males within survivors
    Is *gender* a risk factor?

Yearly Data Comparison: Survivor vs General

Means of Yearly Visit Counts



Means of Yearly Medical Costs



Yearly Data Comparison: survivor with RSC vs. survivor vs. general

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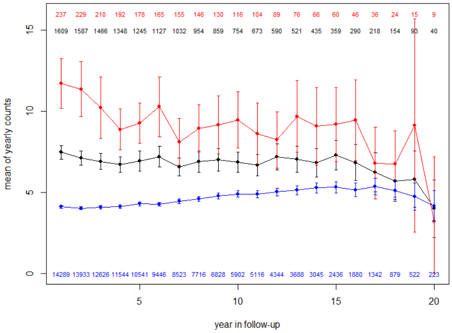

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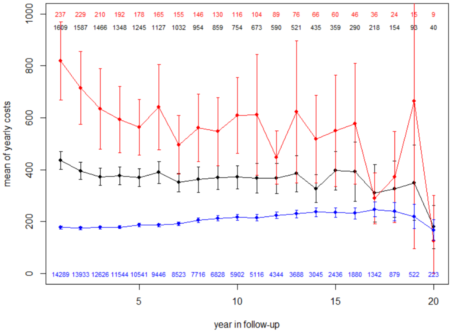

SC with RSC — survivor cohort — general population

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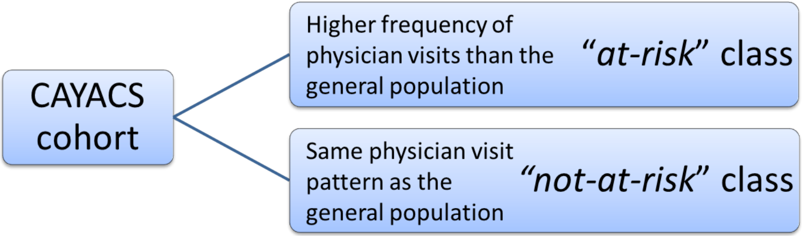

The class membership ($\eta = 1$ or 0) is not observable.

$\Longrightarrow$ to consider a latent class model

Difficulties in Analysis under Latent Class Models

- Increased number of parameters $\rightarrow$ low efficiency
- Underlying probability model specification for each latent class: since no available information directly on η, and thus on $Y|\eta$ $\rightarrow$ lack of robustness to distribution assumptions

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Additional Information

- Supplementary Information: general population (about $\eta = 0$ group?)
- Partially observed at-risk class ($\eta = 1$): a total of 168 survivors with relapse/2nd cancer ($\delta = 1$)

1. Introduction: Statistical Modelling

Model Specification

Risk model

$$P(\eta = 1|\mathbf{Z}) = p(\mathbf{Z}; \alpha)$$

Regression models for each class

$$E(\mathbf{Y}|\eta = 1, \mathbf{Z}) = \mu_1(\mathbf{Z}; \beta)$$

$$E(\mathbf{Y}|\eta = 0, \mathbf{Z}) = \mu_0(\mathbf{Z}; \theta)$$

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$P(\eta = 1|\mathbf{Z}) = p(\mathbf{Z}; \alpha)$ e.g. $\text{logit}\{p(\mathbf{Z}; \alpha)\} = \alpha'\mathbf{Z}$

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Estimation of (α, β, θ) based on data from the *survivor cohort* combined with the sample from the *general population*

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Why bother? *Examples for its use:*

- by $p(\mathbf{Z}; \alpha)$, risk factor identification; risk probability estimation
- by $\mu_1(\mathbf{Z}; \beta)$, visit patterns in *"at-risk"* class
- by $\mu_0(\mathbf{Z}; \theta)$, visit patterns in *"not-at-risk"* class
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How? *Procedures:*

- Likelihood-Based Estimation with Cross-Sectional Counts under Mixture Poisson Models (Wang et al, 2014)
- Extended GEE Procedures with Longitudinal Data

2. Likelihood-Based Estimation with Cross-Sectional Counts: Model Assumption

$\mathbf{Y} = Y$ cross-sectional visit count over $(0, T]$ with T the follow up time.

Mixture Poisson Model

$$
\begin{aligned}
& [Y|\mathbf{Z};\alpha,\beta,\theta] \\
= \ & [Y|\eta=0,\mathbf{Z};\theta][\eta=0|\mathbf{Z};\alpha]+[Y|\eta=1,\mathbf{Z};\beta][\eta=1|\mathbf{Z};\alpha]
\end{aligned}
$$

- $Y|\eta=1,\mathbf{Z} \sim \text{Poisson}\big(\mu_1(\mathbf{Z};\beta)\big)$
- $Y|\eta=0,\mathbf{Z} \sim \text{Poisson}\big(\mu_0(\mathbf{Z};\theta)\big)$
- $\eta=1|\mathbf{Z} \sim$ logistic regression model

2. Likelihood-Based Estimation with Cross-Sectional Counts: Procedures

- **Maximum Likelihood Estimation (MLE)** Likelihood function based on the data from CAYACS cohort $L(\alpha, \beta, \theta; \mathrm{Data}_{\mathcal{P}}) \propto \prod_{i \in \mathcal{P}} [Y_i | \mathbf{Z}_i; \alpha, \beta, \theta]$
  - EM algorithm via the "full-data" likelihood based on $[Y_i, \eta_i | \mathbf{Z}_i]$
  - computationally intense

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- **Pseudo-MLE** With rich information on θ from the general population, likelihood function:

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  Type AB pseudo MLE.
  - $\hat{\theta}$ from $\prod_{i \in \mathcal{Q}} [Y_i | \eta_i = 0, \mathbf{Z}_i; \theta]$
  - $(\hat{\alpha}, \hat{\beta})$ from $\prod_{i \in \mathcal{P}} [Y_i | \mathbf{Z}_i; \alpha, \beta, \hat{\theta}]$

2. Likelihood-Based Estimation with Cross-Sectional Counts: Properties

- Consistency and asymptotic normality
- MLE vs the Pseudo-MLE: efficiency?
- Extended Huber sandwich variance estimator: *e.g.* account for $\hat{\theta}$ estimated from $\mathcal{Q}$

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However,

- Simulation results show that likelihood-based estimators were biased under distribution misspecification, especially for α
- CAYACS physician visit counts are highly overdispersed. Plus physician claims include costs and are longitudinal.

$\Longrightarrow$ to adapt the GEE approach

3. Extended GEE Procedures with Longitudinal Data: Modelling

Consider the Mean-Variance Models:

$$E(Y|\mathbf{Z}) = p(\mathbf{Z};\alpha)\mu_1(\mathbf{Z};\beta) + \{1 - p(\mathbf{Z};\alpha)\}\mu_0(\mathbf{Z};\theta) \equiv \Lambda$$

$$\begin{aligned} V(Y|\mathbf{Z}) = {} & p(\mathbf{Z};\alpha)\Sigma_1 + \{1 - p(\mathbf{Z};\alpha)\}\Sigma_0 \\ & + p(\mathbf{Z};\alpha)\{1 - p(\mathbf{Z};\alpha)\}\{\mu_1(\mathbf{Z};\beta) - \mu_0(\mathbf{Z};\theta)\}^2 \equiv \Sigma \end{aligned}$$

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Directly applying the GEE approach:

$$\sum_{i=1}^{n} \frac{\partial \Lambda_i(\alpha,\beta,\theta)}{\partial(\alpha,\beta,\theta)} \Sigma_i^{-1}[Y_i - \Lambda_i(\alpha,\beta,\theta)] = 0$$

the evaluations of the estimator for (α,β,θ)*?*

3. Extended GEE Procedures with Longitudinal Data: Procedure

- Using the information from the general population to set the standard for "not-at-risk", the group of $\eta = 0$:

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- Using the information from the sub-cohort of subjects with relapse/2nd cancer to set the standard for "at-risk", the group of $\eta = 1$:

$$\sum_{i: \delta_i = 1} \frac{\partial \mu_1(\mathbf{Z}_i; \beta)}{\partial \beta} \Sigma_{1i}^{-1} [Y_i - \mu_1(\mathbf{Z}_i; \beta)] = 0$$

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$\Longrightarrow$ extended GEE estimator with consistency and asymptotic normality: how is it compared with MLE?

3. Extended GEE Procedures with Longitudinal Data: Implementing with CAYACS Data

responses $\mathbf{Y}_i \to Y_{ij}$: $j = 1, \ldots, J_i$, $J_i \in [1, 20]$
yearly visit counts/log-trans costs

potential risk factors
- **sex:** male vs female
- **age at study entry:** 5 years after diag
- **SES:** socioeconomic status, high vs low
- **diagnosis period:** 1990s vs 1980s
- **cancer treatment:** chemotherapy no radiation, radiation no chemotherapy, both vs others

Table 3.1. LCM Analysis: intercept, sex, age at entry – effect time-varying; compound symmetric corr

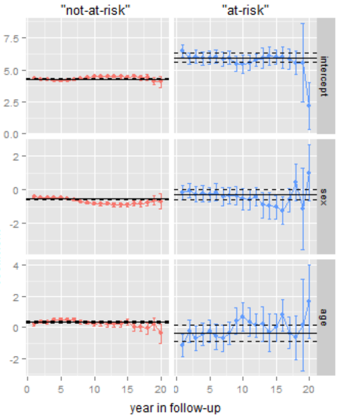
Factor	counts estimate	counts sw.se	costs estimate	costs sw.se
α estimates in the Risk Model				
intercept	0.179	(0.435)	0.196	(0.314)
male (vs female)	-0.329	(0.341)	-0.286	(0.247)
SES high (vs low)	0.365	(0.342)	0.280	(0.248)
age at diagnosis	0.097	(0.590)	-0.302	(0.389)
diag in 90s (vs 80s)	**-1.347**	(0.283)	0.017	(0.178)
treatment (vs other)				
chemo no rad	**0.474**	(0.246)	0.269	(0.181)
rad no chemo	**1.524**	(0.525)	**1.729**	(0.509)
both	**1.463**	(0.413)	**0.946**	(0.241)
β estimates in the Regression Model for the "at-risk" class				
GEE estimates based on $\delta = 1$ subgroup				
intercept	**2.360**[b]	(0.128)[c]	**5.664**[b]	(0.232)[c]
male (vs female)	**-0.293**[b]	(0.124)[c]	**-0.421**[b]	(0.201)[c]
SES high (vs low)	-0.078	(0.111)	-0.094	(0.159)
age at study entry	0.070[b]	(0.186)[c]	-0.071[b]	(0.287)[c]
dispersion/scale parameter	**10.59**	(1.302)	**2.641**[b]	(0.224)[c]
correlation parameter	**0.331**	(0.042)	**0.401**	(0.048)
θ estimates in the Regression Model for the "not-at-risk" class				
GEE estimates based on general population				
intercept	**1.537**[b]	(0.036)[c]	**4.324**[b]	(0.032)[c]
male (vs female)	**-0.546**[b]	(0.040)[c]	**-0.697**[b]	(0.030)[c]
SES high (vs low)	**-0.062**	(0.019)	**-0.049**	(0.020)
age at study entry	**0.399**[b]	(0.060)[c]	**0.235**[b]	(0.047)[c]
dispersion/scale parameter	**10.029**	(0.537)	**2.801**[b]	(0.025)[c]
correlation parameter	**0.381**	(0.013)	**0.333**	(0.005)

[a]Significant Effect with P-value $\leq$ 0.05 in **Boldface**

[b]Average values over 20 estimates

[b]se of the 20 averaged estimate

Time-varying coefficients: (yearly costs)



4. Application to Risk Classification and Prediction

Statistical Modelling II

To capture heterogeneity within individual ...

$$l\Big\{\mathrm{E}\big(Y_{ij}\big|\eta_i = 1, Z_{ij}, b_i\big)\Big\} = \beta_j' Z_{ij} + b_i' X_{ij}$$

$$l\Big\{\mathrm{E}\big(Y_{ij}\big|\eta_i = 0, Z_{ij}, c_i\big)\Big\} = \theta_j' Z_{ij} + c_i' X_{ij}$$

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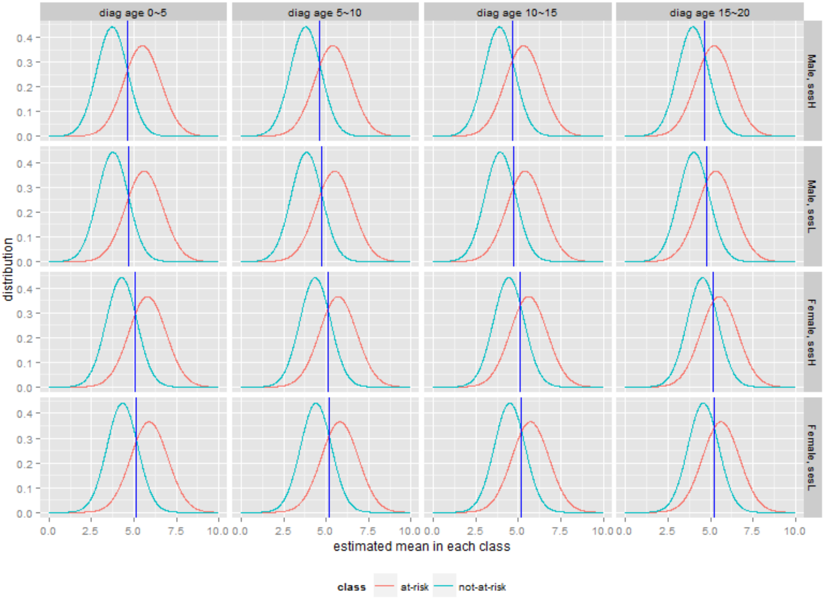
Special cases:

(i) $X_{ij} = 1 \Longrightarrow b_i$ and c_i are scalar ("random intercept")

(ii) for cost $\Longrightarrow l\{\} = I$; for count $\Longrightarrow l\{\} = \log$



Application A. Risk Classification by Yearly Costs Using $E(\mathbf{Y}_i|\mathbf{Z}_i, \hat{b}_i, \hat{c}_i)$

Application B. Risk Classification based on Estimated Risk Probabilities

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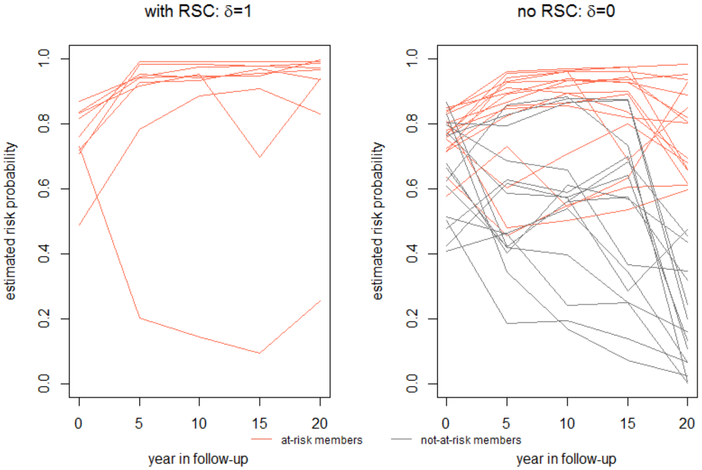
(A) jointly model $\mathbf{Y}$ and η via b and c
(B) to approximate it by

$$\frac{[\mathbf{Y}_i|\eta_i = 1, \mathbf{Z}_i, b_i]P(\eta_i = 1|\mathbf{Y}_i, \mathbf{Z}_i)}{[\mathbf{Y}_i|\eta_i = 1, \mathbf{Z}_i, b_i]P(\eta_i = 1|\mathbf{Y}_i, \mathbf{Z}_i) + [\mathbf{Y}_i|\eta_i = 0, \mathbf{Z}_i, c_i]P(\eta_i = 0|\mathbf{Y}_i, \mathbf{Z}_i)}$$

Histograms of estimated risk probabilities for full survivor cohort and parametric bootstraps

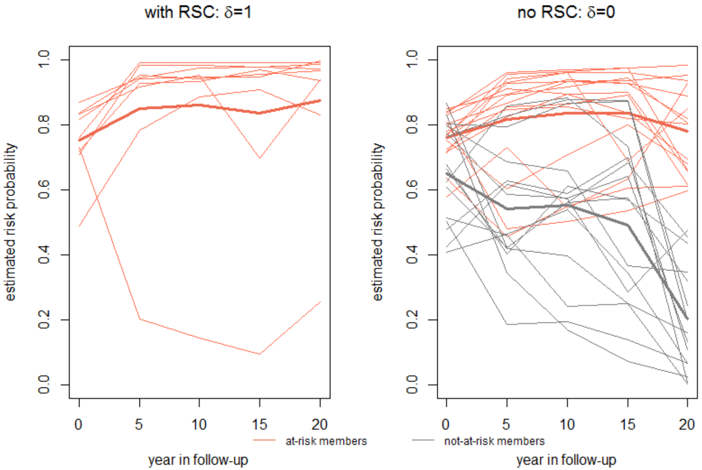
$\hat{P}(\eta_i = 1|\mathbf{Z}_i)$ $\hat{P}(\eta_i = 1|\mathbf{Y}_i, \mathbf{Z}_i)$ $\hat{P}(\eta_i = 1|\mathbf{Y}_i, \mathbf{Z}_i, b_i, c_i)$

Dynamic risk probabilities:
40 survivors diagnosed in 1981 and followed until 2006



$$P(\eta = 1|\mathbf{Z}) \mapsto P(\eta = 1|\mathbf{Z}, \mathbf{Y}_5) \mapsto P(\eta = 1|\mathbf{Z}, \mathbf{Y}_{10}) \mapsto P(\eta = 1|\mathbf{Z}, \mathbf{Y}_{15}) \mapsto P(\eta = 1|\mathbf{Z}, \mathbf{Y}_{20})$$

Dynamic risk probabilities:
40 survivors diagnosed in 1981 and followed until 2006, with estimated means for the two classes



Thanks for your attention!