Causal mediation analysis of observational, population-based cancer survival data

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Outline

• Main questions
• Challenges with conventional approaches – results from the past
• An example of applying mediation to cancer survival data
• Challenges and discussions
  – Misclassification of mediators
    • Treatment missing for more affluent – sensitivity analysis
    • Under-staged deprived patients – sensitivity analysis
  – Biases for mediation analyses
  – Controlled and natural effects
  – Conceptual frameworks – Suggestions?
Inequalities in cancer survival

Annual number of avoidable deaths

Calendar period of diagnosis

2004-2006

1 in 3 are diagnosed
#RETHINKCANCER
Explaining inequalities
Challenges in the past

• More deprived patients:
  – More comorbidity
  – More advanced cancer at diagnosis (colon, rectum, breast)
  – More often diagnosed during emergency admission
  – More often treated in non-specialised hospital and by non-specialised surgeon
  – Received more often sub-optimal and delayed treatment (colon, rectum)

• Past conventional analysis (colon, rectum, breast)
  – No excess mortality hazard for deprivation among those treated within one month since diagnosis
  – Adjusting for comorbidity did not modify the excess mortality hazard for deprivation
  – Adjusting for stage reduced the excess mortality hazard for deprivation by less than a third
  – Limited stage and treatment data and conventional analytic approaches did not enable identification of mechanisms underlying deprivation gap in survival
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How much of the socioeconomic differences in breast cancer patient survival can be explained by stage at diagnosis and treatment?

Application of causal mediation analysis to routine data

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Introducing breast cancer

• Most common cancer in the UK
• Screening (50-70)
• Treatment with strict guidelines

• Northern and Yorkshire Cancer Registry, population-based, covering 12% of the English population

• Women with malignant breast cancers (N=36,793)
  – Diagnosed during the period 2000–2007
  – Followed up until 31 December 2007
Large deprivation gap in survival from breast cancer...
Possible explanations

- Differential stage at diagnosis?
- Differential treatment?
Differential stage at diagnosis?

<table>
<thead>
<tr>
<th>Stage</th>
<th>All patients</th>
<th>Least deprived</th>
<th>Most deprived</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>38%</td>
<td>41%</td>
<td>36%</td>
</tr>
<tr>
<td>II</td>
<td>42%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>III</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>IV</td>
<td>5%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Missing</td>
<td>8%</td>
<td>6%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Differential treatment?  
– probability of getting major surgery

15-49 pre-screening

50-69 screening

70+ post-screening

- Most affluent
- 2
- 3
- 4
- Most deprived
Linking to the conceptual diagram...
If we look at stage

We can decompose the total effect (TCE) of socioeconomic status (deprivation) on mortality into...

- Those mediated by stage (The indirect effect, NIE)
- Those not mediated by stage (The direct effect, NDE)

\[
\text{TCE} = \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Stage}(\text{Dep}=\text{most})))) - \log(\text{odds}(Y(\text{Dep}=\text{least}, \text{Stage}(\text{Dep}=\text{least}))))
\]

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\text{NIE} = \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Stage}(\text{Dep}=\text{most})))) - \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Stage}(\text{Dep}=\text{least}))))
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\]
If we look at treatment

We can decompose the total effect (TCE) of deprivation on mortality into...

- Those mediated by treatment (The indirect effect, NIE)
- Those not mediated by treatment (The direct effect, NDE)

\[
\text{TCE} = \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Treat}(\text{Dep}=\text{most})))) - \log(\text{odds}(Y(\text{Dep}=\text{least}, \text{Treat}(\text{Dep}=\text{least}))))
\]

\[
\text{NIE} = \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Treat}(\text{Dep}=\text{most})))) - \log(\text{odds}(Y(\text{Dep}=\text{most}, \text{Treat}(\text{Dep}=\text{least}))))
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\]
G-formula results

6 months  12 months  3 years  5 years

Total effect

Effect via stage

Effect via treatment
Preliminary conclusions

• Breast cancer survival differed between the most deprived and most affluent patients

• Effect of deprivation on mortality:
  – Large total effect FOR ALL DEPRIVATION CATEGORIES:
    • Increasing with deprivation
    • Decreasing with time since diagnosis
  – Mediated via stage ONLY FOR MOST DEPRIVED CATEGORY:
    • One third of at six months
    • One tenth at three/five years since diagnosis
  – Mediated via treatment:
    • None
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Misclassification of stage

- More deprived patients may be under-staged?
- Randomly “up-staging” 10%, 30% and 50% of most deprived patients...
- 10% up-staging did not change results much
- After 30%-50% upstaging, stage would mediate more than half of the survival differences
- Longer-term survival is more affected...

Most deprivation vs least deprived, proportion of patients upstaged
Misclassification of treatment

• One report showed that 4% of surgical treatment for breast cancer were made in private hospital

• Sensitivity analysis:
  – Assumption: all missing surgery is among most affluent patients
  – Randomly adding “major surgery” to 4% of women, all from the most affluent category

• Now treatment mediates survival differences for the most deprived!
Biases for mediation analysis

- Unmeasured or poorly measured confounders, e.g., between mediator and outcome?
- Presence of confounder(s) between mediator and outcome affected by exposure?
Summary

• First application of the causal mediation tool in study of cancer registry data
• Population-based data
• Drawbacks
  – Data quality and detail
  – Unmeasured confounder, e.g. comorbidity
• Useful for answering questions related to causality
  – Resource allocation
References

Questions for you

• How to deal with the potential biases, due to unmeasured/poorly measured confounders?
• Controlled vs. natural effects?
• How to deal with stage misclassification?
• Suggestions on the research questions or the frameworks?