Effect of Celecoxib on Adenoma Count using a Zero-inflated Poisson (ZIP) Model with Random Effects

Meier Hsu, Ann Zauber, Mithat Gönen, Monica Bertagnolli

Memorial-Sloan Kettering Cancer Center

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Background

- Colorectal cancer (CRC) is the second leading cause of cancer deaths in the US
- CRC is one of the most preventable cancers
  - Most CRC develop from precursor adenomas which can be identified and removed during screening colonoscopy
- NSAIDs, including aspirin, may reduce the incidence of adenomas, CRC, and deaths from CRC
  - NSAIDs are non-specific inhibitors of cyclooxygenases (COX)
  - Overexpression of COX2 can lead to oncogenic responses
- Celecoxib (Celebrex) is a COX2-specific inhibitor used for treatment of arthritis
- Several clinical trials were launched in 1999-2000 to study effect of Celecoxib on prevention of adenomas
Design of Adenoma Prevention with Celecoxib (APC)

Men and women age 30 or older with large or multiple colorectal adenomas

2035 patients randomized to:

- **celecoxib 200mg bid** N=685
- **celecoxib 400mg bid** N=671
- **placebo bid** N=679

*stratified by low-dose aspirin use and clinical center*

Study medication continued for 3 years after randomization

Colonoscopy at 1 and 3 years after randomization

**Primary Endpoint:** Adenoma detected at any post-randomization colonoscopy
Detection of any adenoma on follow-up colonoscopy

- Placebo bid
- Celecoxib 200 mg bid
- Celecoxib 400 mg bid

Risk Ratio (95% CI)

* p<0.0001 compared to placebo

All patients

Risk Ratio (95% CI)

Bertagnolli, Hawk, Eagle NEJM 2006
Secondary Analysis for APC

Outcome: Number of adenomas detected by colonoscopy

- Objectives
  - Compare treatments
  - Predict adenoma counts at follow-up

- Covariates of interest:
  - Treatment
  - Number of adenomas at baseline
  - Year of surveillance colonoscopy

Model considerations:
- 2 follow-up observations per patient
  - Poisson with random effect
# Observed Adenoma Counts Post-randomization

<table>
<thead>
<tr>
<th>No. of adenomas</th>
<th>Year 1</th>
<th>Year 3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1228 (67.4%)</td>
<td>1075 (69.8%)</td>
<td>2303 (68.5%)</td>
</tr>
<tr>
<td>1</td>
<td>372 (20.4%)</td>
<td>287 (18.6%)</td>
<td>659 (19.6%)</td>
</tr>
<tr>
<td>2</td>
<td>125 (6.9%)</td>
<td>111 (7.2%)</td>
<td>236 (7.0%)</td>
</tr>
<tr>
<td>3</td>
<td>52 (2.9%)</td>
<td>36 (2.3%)</td>
<td>88 (2.6%)</td>
</tr>
<tr>
<td>4</td>
<td>16 (0.9%)</td>
<td>17 (1.1%)</td>
<td>33 (1.0%)</td>
</tr>
<tr>
<td>5+</td>
<td>29 (1.6%)</td>
<td>15 (1.0%)</td>
<td>44 (1.3%)</td>
</tr>
</tbody>
</table>
Predicted Poisson counts compared to observed

Number of adenomas

- Observed
- Poisson*

* Poisson model of treatment + year + baseline count + random effect

✱ Poisson is a poor fit of the data
Zero-inflated Poisson (ZIP) model with random effects

\[
\Pr(y_{ij}) = (1 - \pi_{ij}) f(y_{ij}) + I(y_{ij} = 0)\pi_{ij} \quad \text{where} \quad f(y_{ij}) = \frac{e^{-\lambda_{ij}} \lambda_{ij}^{y_{ij}}}{y_{ij}!}
\]

\[
\begin{cases} 
\text{when } y = 0, & \pi_{ij} + (1 - \pi_{ij}) e^{-\lambda_{ij}} \\
\text{when } y > 0, & (1 - \pi_{ij}) \frac{e^{-\lambda_{ij}} \lambda_{ij}^{y_{ij}}}{y_{ij}!}
\end{cases}
\]

are modeled with

\[
\text{Logit}(\pi_{ij}) = \gamma' w_{ij} + \nu_i
\]

\[
\text{Log}(\lambda_{ij}) = \beta' x_{ij} + \nu_i
\]

\(y_{ij}\) response variable for the \(j^{th}\) colonoscopy of the \(i^{th}\) individual
\(x_{ij}\) and \(w_{ij}\) are the vector of known covariates for Poisson and logistic
\(\beta\) and \(\gamma\) are the Poisson and logistic regression parameters
\(\pi_{ij}\) is a mixing parameter for the mixture of a binary and a Poisson process
\(\nu_{i}\) and \(\nu_{i}\) are random effects assumed to be \(\nu_{i} \sim N(0, \sigma_{1}^{2})\) and \(\nu_{i} \sim N(0, \sigma_{2}^{2})\)
How ZIP can better fit our data

**Poisson**

- Poisson, $\lambda=1$

**ZIP**

- $\pi$*Poisson, $\pi=0.2$, $\lambda=1$
- $(1-\pi)$*Poisson, $\pi=0.2$, $\lambda=1$
ZIP predicted counts versus observed

*Poisson model of treatment + year + baseline count + random effect
**ZIP model with the same covariates in both submodels

- ZIP model fits the observed data better than the Poisson
### Parameter Estimates of ZIP with random effects model

Table 1: Zero-inflated Poisson model regressing number of adenomas upon all variables shown

<table>
<thead>
<tr>
<th>Variables</th>
<th>Logistic (γ)</th>
<th>Poisson (β)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.115</td>
<td>0.57</td>
</tr>
<tr>
<td>200 mg (vs placebo)</td>
<td>-0.495</td>
<td>0.52</td>
</tr>
<tr>
<td>400 mg (vs placebo)</td>
<td>-0.655</td>
<td>0.60</td>
</tr>
<tr>
<td>year 3 (vs year 1)</td>
<td>0.323</td>
<td>0.39</td>
</tr>
<tr>
<td># adenomas at baseline</td>
<td>1.08</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Estimated mean adenoma counts

- Mean adenoma count is consistently lower on celecoxib than placebo (p<.0001)
- Mean adenoma count increases with increasing number of adenomas at baseline (p<.0001)
Year 3 colonoscopy overall has lower estimated mean counts than year 1 (p=0.03)
Conclusions

- ZIP with random effects demonstrates a better model fit of the data than the Poisson model.
- Parameter estimates from ZIP do not have direct clinical interpretation, however the model is still clinically relevant.
- Celecoxib significantly reduces expected adenoma count in a dose-dependent manner, compared to placebo.
- Baseline adenoma count is significantly associated with the number of adenomas detected at follow-up.
- Expected adenoma count at year 3 is also significantly lower than at year 1.
References

APC trial results:


ZIP with random effects papers:

Yau KK and Lee AH. Zero-inflated Poisson regression with random effects to evaluate occupational injury prevention programme. Statist Med; 2001; 20:2907-2920

Analysis using SAS:
hsum1@mskcc.org
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