**Cohort Studies**

Linda Zangwill, Ph.D.  
Hamilton Glaucoma Center  
Department of Ophthalmology  
UC San Diego

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**Definition of Cohort Study**  
(Also known as longitudinal, follow-up, or prospective study)

- Follow-up of exposed and non-exposed defined groups, with a comparison of disease rates during the time covered.
Design of a Cohort Study

Exposed
- Develop Disease
- No Disease

Not exposed
- Develop Disease
- No Disease

Design of a Cohort Study
(Can study multiple diseases)

Exposed
- Develop Disease A
- No Disease A
- Disease B
- No Disease B
- Disease C
- No Disease C

Not exposed
- Develop Disease A
- No Disease A
- Disease B
- No Disease B
- Disease C
- No Disease C

Two types of Cohort Studies

Concurrent: 2005 Defined Population
2010 Exposed vs Not Exposed
2005 Disease
2005 No Disease

Retrospective: 1995
Cohort Study

Advantages
• Incidence rates can be calculated
• Precise exposure measurement possible
• Temporal relationship between exposure and disease easily established
• Many disease outcomes studied simultaneously
• Possible to study multiple exposures when population selected on factor unrelated to exposure

Limitations
• Expensive
• Long duration
• Large sample needed
• Not optimal for rare disease
• Selection of non-exposed comparison group often difficult
• Loss to follow-up

Framingham Study
Early cohort study
• Possible to study multiple exposures when population selected on factor unrelated to exposure
• Studied many exposures such as weight, blood pressure, smoking, cholesterol levels and physical activity

Definition of Case-Control Study
(Also known as retrospective study)
• Retrospective comparison of exposures of persons with disease (cases) with those of persons without the disease (controls).
Case Control Studies

Exposed | Not Exposed | Exposed | Not Exposed
---|---|---|---
Disease | No Disease | No Disease | Disease

Case-Control Study

Advantages
- Relatively inexpensive
- Shorter duration
- Desirable when disease occurrence is rare
- Many exposures studied simultaneously

Limitations
- Incidence rates cannot be calculated
- Relative risk cannot be calculated (estimated with odds ratios)
- Bias in exposure measurement possible (recall bias)
- Temporal relationship between exposure and disease not easily established
- Not optimal for rare exposures
- Selection of non-diseased comparison group often difficult

Cohort Study

Case Control Study

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>
See handout

Principal Investigators:
- Pamela Sample: Visual Function NIH EY08208
- Linda Zangwill: Structural Assessment NIH EY11008

DIGS Co-Investigators:
- Robert Weinreb, M.D.
- Christopher Bowd, Ph.D.
- Catherine Boden, Ph.D.
- Felipe Medieros, M.D.
- Charles C. Berry, Ph.D.
**DIGS Objectives:**

To Characterize
- Structural and Functional Damage and Progression in Glaucoma
- Rates and Patterns of Progressive Glaucomatous Damage

**DIGS**
(Diagnostic Innovations in Glaucoma Study)

**Inclusion Criteria**

**Exposures**

- Multiple Diseases
  - 1) Development of POAG
    - Or
    - 2) Progressing POAG
  - 1) No Development of POAG
    - Or
    - 2) Non-progressing POAG

**DIGS**

* Most publications to date have been cross-sectional
* Need long duration for sufficient number of endpoints
Examples of published cohort analyses

**Examples of published cohort analyses**

- **Exposures**: Convert eyes: ≥ 3 consecutive abnormal VF during follow-up
- **Disease**: Non-convert eyes: < 3 consecutive abnormal VF during follow-up

226 Subjects Met Inclusion Criteria:

- Age ≥ 40 years
- Minimum follow-up of 2 years (mean: 4 years)
- Good quality baseline HRT image and photograph
- Normal standard automated perimetry (SAP) results at baseline HRT (CPSD and GHT within normal limits)
- Optic disc appearance was not used to determine eligibility

Visual Field Endpoint: Standard Automated Perimetry (SAP)

- 37 eyes converted to glaucomatous SAP VF
  - ≥ 3 consecutive, reliable, "glaucomatous" SAP VF, based on CPSD / PSD and / or GHT outside normal limits
- 189 eyes did not convert to glaucomatous SAP VF
  - < 3 consecutive SAP VF outside normal limits
Significant Baseline Predictive Factors from Univariate Proportional Hazards Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT Predictors</td>
<td>SAP MD (per 1 dB lower)</td>
<td>1.3 (1.0, 1.6)</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>SAP PSD (per 1 dB higher)</td>
<td>3.0 (1.2, 7.6)</td>
<td>.024</td>
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<tr>
<td>Stereophotograph Predictors</td>
<td>RNFL Thickness (per 0.1 mm thinner)</td>
<td>1.6 (1.0, 2.5)</td>
<td>.043</td>
</tr>
<tr>
<td></td>
<td>Moorfields Nasal Sup (ONL vs WNL)</td>
<td>2.8 (1.3, 5.7)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>Horiz. Cup Disc Ratio (per 1 higher)</td>
<td>2.9 (1.4, 5.9)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>Vert. Cup Disc Ratio (per 1 higher)</td>
<td>1.2 (1.0, 1.5)</td>
<td>.100</td>
</tr>
</tbody>
</table>

There were several similar Multivariate Proportional Hazards Models with 2 variables

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: HRT and SAP</td>
<td>SAP MD (per 1 dB lower)</td>
<td>1.3 (1.0, 1.6)</td>
</tr>
<tr>
<td></td>
<td>Moorfields Nasal Sup (ONL vs WNL)</td>
<td>2.9 (1.4, 6.2)</td>
</tr>
<tr>
<td>Model 2: photo &amp; SAP</td>
<td>SAP MD (per 1 dB lower)</td>
<td>1.3 (1.0, 1.5)</td>
</tr>
<tr>
<td></td>
<td>Stereophotograph: &quot;Glaucomatous vs Normal&quot;</td>
<td>2.6 (1.3, 5.5)</td>
</tr>
<tr>
<td>Model 3: photo and HRT</td>
<td>Moorfields Nasal Sup (ONL vs WNL)</td>
<td>2.0 (0.8, 4.7)</td>
</tr>
<tr>
<td></td>
<td>Stereophotograph: &quot;Glaucomatous vs Normal&quot;</td>
<td>2.3 (1.0, 5.6)</td>
</tr>
<tr>
<td>Model 4: photo and HRT</td>
<td>RNFL Thickness (per 0.1 thinner)</td>
<td>1.6 (0.8, 2.9)</td>
</tr>
<tr>
<td></td>
<td>Stereophotograph: &quot;Glaucomatous vs Normal&quot;</td>
<td>2.6 (1.3, 5.4)</td>
</tr>
</tbody>
</table>

Cumulative Survival Curves for Significant Independent Predictors in Multivariate Models
**Major Sources of Bias in Cohort Studies**

- Bias in ascertainment of outcome: If persons who decides disease status knows exposure status and hypothesis, may have biased judgment
  - Precise assessment (visual fields well characterized)
  - Masked to exposure status

- Information bias: If quality and extent of information obtained is different for exposed and unexposed
  - Did not need to ‘select’ an exposed and unexposed group, came from same-source-DIGS population
  - Precise assessment of exposure possible (imaging, risk factors etc)

**Major Sources of Bias in Cohort Studies**

- Bias from nonresponse and loss to follow-up: Are those that choose to participate (agree) and remain in study (continue medical care at clinic) different from those who do not?
  - Change in insurance: Established research clinic for those no longer seen in clinic

- Analytic bias: Preconceptions of investigators who are analyzing the data may unintentionally introduce biases into their analyses and interpretation of results
  - Financial disclosure
  - Non-financial investment

**Other Methodological Issues**

*study designed to reduce possible sources of bias*

- Source population
  - Not population based
  - May not be representative of general glaucoma population

- Inclusion criteria
  - No optic disc criteria
  - Informally may influence
Methodological issues related to studying diagnostic techniques: Evidence based medicine recommendations

- Independent gold standard
  - For imaging studies, based on visual field and not optic disc damage
- Gold standard applied similarly regardless of participants’ disease status or test result
  - All participants get tested in a similar manner
- Include participants with diagnostic uncertainty
  - Early glaucoma included
  - Are healthy comparison group “super normals?”
- Present data as likelihood ratios

Likelihood ratio

Pre-test probability of glaucoma

IMAGING TEST

How much does the test change the probability of disease?

Post-test probability of glaucoma?

Probability of test result in patients WITH disease

Probability of test result in patients WITHOUT disease

- LR = 1: Test result provides no additional information
- LR > 1: Test result increases the likelihood of disease
  - LR ≥10: Large effect
  - 5 ≤ LR < 10: Moderate effect
  - 2 ≤ LR < 5: Small effect
  - 1 ≤ LR < 2: Insignificant effect
Comparison of GDx VCC, HRTII and Stratus OCT for the Detection of Glaucoma
Medieros, Zangwill, Bowd & Weinreb Arch Ophthalmol 2004: 122; 821-831

Discussion and Thank You