BE.104 Spring
Putting it all together: Critical review of EHS studies
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Outline
I. Historical studies
    A. Age-adjusted
    B. Age-cohort
II. Evaluation of study examples

I.A. Historical analyses – age-adjusted

NIH-NCI SEER Data
"Surveillance, Epidemiology, and End Results"
http://seer.cancer.gov/

Review Fig. 1 and Fig. 2 in Proctor, R. N. "Tobacco and the global lung cancer epidemic." Nature Reviews Cancer 1 (October 2001): 82-86.

- What is our level of confidence that lung cancer incidence is increasing for reasons other than chance?

  Why?

- What is responsible for the change in mortality/incidence (risk) with time?

- Does age-adjustment take care of all differences due to differences in the age distribution of the population over time? Given that these cancers primarily affect

the elderly, how might the elderly in 2000 differ from the elderly in 1970, e.g.?

I.B. Historical Analyses – age cohort

Figs. 3 and 4

Age-specific cohort incidence (horizontal)

Time-specific population incidence (vertical)

For the same geographic region, indicates changes in environment, because in general (without population migration) genes do not change this rapidly.

Historical analysis of tobacco-cancer causation
Figs. 5 and 6

Case I
See: Hunt, P. A., et al. "Bisphenol A Exposure Causes Meiotic Aneuploidy in the Female Mouse." Current Biology 13 (April 1, 2003): 546–553.

An accident among mice identifies new reproductive toxin

- Accidental exposure to bisphenol A (BPA) 2,2-(4,4-dihydroxy-diphenol)propane

- Manufacturing agent for polycarbonate plastics and epoxy resins

- Known estrogenic

- Meiotic toxicity

- Damaged plastic caging and bottles as source?

Suspicion:

Laboratory engaged in mouse meiosis research

August 1998 – *suddenly?*

1) frequency of "spontaneous" meiosis defects increased from 1-2% of oocytes to 40%; **p < 0.001**

2) aneuploidy increased from 0.7% to 5.8%; **p < 0.001**

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See Fig. 2 in [Hunt2003].

Coincidences:

- No changes in experimental solutions for meiosis assays
- Recent inadvertent use of harsh alkaline detergent which damage cages and water bottles
- BPA known to leach from polycarbonate

Hypothesis:

Leaching BPA responsible for toxicity in mouse colon?

Cause and Effect Studies:

Are damaged bottles necessary?

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See Fig. 3 in [Hunt2003].

1. Before the washing error
2. During the washing error
3. After the error was noted
4. After removal of the colony to another facility; no polycarbonate ware; and new breeding stock

Are they done?

What kind of study design is this?

Next:

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See Table 2 in [Hunt2003].

What kind of study is this?

Any bias?

Are they done now?

Next:

1. Showed that BPA is in fact in the water of damaged bottles

2. Estimated daily dose

3. Dose the mice

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See Table 3 in [Hunt2003].

(6-8 days; **p < 0.05?**)

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See Fig. 5 in [Hunt2003].

(20ng/g; **p < 0.05?**)

What happened?!
What type of statistical error should we be concerned about?

Human exposure concern?

Case II

And now a human study:

Hecht, S. S., et al. "Metabolites of a Tobacco-specific Lung Carcinogen in the Urine of Elementary School-aged Children." Cancer Epidemiology, Biomarkers & Prevention 10, (November 2001) 1109–1116.

Concern: Are children exposed to carcinogens in environmental tobacco smoke (ETS)?

1.2 RR in adults for lung cancer

(Compared to 10-20 RR for smokers)

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) tobacco smoke-specific carcinogen

NNAL and NNAL-Gluc are metabolite indicators of exposure found in urine

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See Figure 1 in [Hecht2001].

Also cotinine and cotinine-gluc, non-carcinogenic ETS exposure indicators

Study design:

IRB-approved

Elementary school age children (grades 2-5; 48% female)

Random sampled from school enrollment data
Minnesota Public Schools, but only two schools used

First a recruitment/explanation letter sent

Next recruiter visits with family

Verbal and written consent

Questionnaire about smoking practices

Designate child as exposed or non-exposed

Get urine sample from child at school with nurse assistance
Some only one; others two

Measure metabolites

Relate metabolite levels to exposure status

What kind of study is this?
Any sources of bias?
Any sources of error?

Results:

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See Figure 2 in [Hecht2001].

Cotinine distribution for all children
What could account for it?

Setting up a contingency table:

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See Table 1 in [Hecht2001].

What is the test of choice?
How well does cotinine predict NNK exposure?

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See Table 5 in [Hecht2001].

Pearson Product Moment Correlation Coefficient

What does r = 0.71 mean?

How good is the correlation?

How significant is the association?

CI's and geometric means

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See Table 2 in [Hecht2001].

Comparing distributions

Image removed for copyright reasons.
See Figure 6 in [Hecht2001].

And a built-in meta analysis:

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See Table 4 in [Hecht2001].