Clinical Epidemiology: Evidence of Risk and Harm
Patients encounter (possibly) risky exposures

- Alcohol during pregnancy (fetal risk)
- Electromagnetic fields (cancer risk)
- Vasectomy (prostate cancer risk)
- Oral contraceptives (thromboembolism risk)
To examine such risks

• Evaluate validity of data
• Evaluate strength of association between risk and outcome
• Evaluate relevance to particular individuals
Most studies of risk are observational studies

• These studies are nonrandomized
• Need:
  • Basic rules of evidence for nonrandomized studies
  • Pitfalls to which observational studies are prone
Types of observational studies

- Cohort studies
- Case-control studies

In each case, we need

- Well-defined outcome
- Well-defined exposure
- Clearly identified comparison groups
- Similarity between groups wrt all other factors that might affect the outcome
Compare to randomized trial

• Well-defined outcome: Primary endpoint
• Well-defined exposure: Active treatment
• Clearly identified comparison groups: Control group for comparison
• Similarity between groups wrt all other factors that might affect the outcome: Randomization
Cohort studies

- Prospective
- Useful when pts cannot be randomized to exposure
- Identify groups of exposed and non-exposed
- Follow forward to determine rate of outcome in each group
Example of question for cohort study

• Do operating room personnel suffer higher rates of miscarriage than do others?
  • Outcome
  • Exposure
  • Clearly identified comparison groups
  • Similarity between groups re outcome
Problems with cohort studies

- Primary issue: self-selection to group
- Same factors that affect selection might also affect outcome
- Example: relationship of NSAIDs to GI bleeding
  - Increased age associated with increased use of NSAIDs
  - Increased age associated with increased GI bleeding
- Age here is a “confounding variable”
  - Document differences
  - Adjust for statistically (regression)
Relative strength of evidence: RCT & Cohort

• Can never rule out the presence of unidentified confounders
• A good cohort study requires a great deal of investigator ingenuity
  • Identify possible biases
  • Document and/or adjust for potential biasing factors
• Thus, cohort studies are inherently less convincing than well-conducted clinical trials
Case-control studies

- Retrospective
- Useful in assessing risks for very rare outcomes
- Useful when time between exposure and risk is long
  - in utero exposure to DES, clear-cell adenocarcinoma of the vagina
  - asbestos, mesothelioma
- Identify persons with the outcome of interest ("cases")
- Identify similar individuals ("controls") who
  - do not have outcome
  - are similar wrt all other factors associated with outcome
- Compare frequency of exposure between groups
Example of question for case-control study

• What exposures predispose to lung cancer?
  • Outcome
  • Exposure
  • Clearly identified comparison groups
  • Similarity between groups re outcome
Problems with case-control studies

• Susceptibility to unmeasured confounders
• Outcome = identified with outcome of interest
  • Ascertainment bias
• Exposure = retrospective documentation of exposure
  • Recall bias
  • Interviewer bias
• Strength of C-C evidence is inherently more limited than cohort study
Second primary guide:

• Were the exposures and outcomes measured in the same way in the groups being compared?
  • RCT, cohort: ascertainment of outcome
  • Case-control: ascertainment of exposure
Secondary guides

- Is the temporal relationship correct?
- Is there a dose-response gradient?
Measuring the association between exposure and outcome

- Most common and useful: relative risk = \( \frac{p_1}{p_2} \)
- Exposure to encainide was associated with a 2.6-fold elevation in risk of death
- Can obtain relative risk from cohort studies or RCT (prospective)
Case-control studies: No RR estimate

- CC studies cannot produce an estimate of the relative risk
- \( RR = \frac{a}{a+b} \times \frac{c}{c+d} \)
- \( OR = \frac{a/b}{c/d} = \frac{ad}{bc} \)
- When outcome is rare, \( OR \approx RR \)
Assessing applicability

- Recall that the number needed to treat (NNT) depends on the absolute risk difference, not the relative risk
- Need to know something about the prevalence of the bad outcome
Outcome: CC Adeno CA  
Exposure: Maternal Smoking

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OR = 3.7  
p = 0.50
Outcome: CC Adeno CA
Exposure: Any prior pregnancy loss

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OR = 16.2
p = 0.01
Outcome: CC Adeno CA  
Exposure: In utero estrogen

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OR 300-400  
p < 0.0001