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# Outline

- 1 Odds ratios for retrospective studies
- 2 Odds ratios approximating the prospective RR
- 3 Exact inference for the odds ratio

## Case-control methods

Smoker	Lung cancer		Total
	Cases	Controls	
Yes	688	650	1338
No	21	59	80
	709	709	1418

- Case status obtained from records
- Cannot estimate  $P(\text{Case} \mid \text{Smoker})$
- Can estimate  $P(\text{Smoker} \mid \text{Case})$

## Continued

- Can estimate odds ratio b/c

$$\begin{aligned} & \frac{Odds(case \mid smoker)}{Odds(case \mid smoker^c)} \\ = & \frac{Odds(smoker \mid case)}{Odds(smoker \mid case^c)} \end{aligned}$$

$C$  - case,  $S$  - smoker

$$\begin{aligned}
 & \frac{Odds(\text{case} \mid \text{smoker})}{Odds(\text{case} \mid \text{smoker}^c)} \\
 = & \frac{P(C \mid S)/P(\bar{C} \mid S)}{P(C \mid \bar{S})/P(\bar{C} \mid \bar{S})} \\
 = & \frac{P(C, S)/P(\bar{C}, S)}{P(C, \bar{S})/P(\bar{C}, \bar{S})} \\
 = & \frac{P(C, S)P(\bar{C}, \bar{S})}{P(C, \bar{S})P(\bar{C}, S)}
 \end{aligned}$$

Exchange  $C$  and  $S$  and the result is obtained

- Sample  $OR$  is  $\frac{n_{11}n_{22}}{n_{12}n_{21}}$
- Sample  $OR$  is unchanged if a row or column is multiplied by a constant
- Invariant to transposing
- Is related to  $RR$

## Notes continued

$$\begin{aligned}
 OR &= \frac{P(S | C)/P(\bar{S} | C)}{P(S | \bar{C})/P(\bar{S} | \bar{C})} \\
 &= \frac{P(C | S)/P(\bar{C} | S)}{P(C | \bar{S})/P(\bar{C} | \bar{S})} \\
 &= \frac{P(C | S) P(\bar{C} | \bar{S})}{P(C | \bar{S}) P(\bar{C} | S)} \\
 &= RR \times \frac{1 - P(C | \bar{S})}{1 - P(C | S)}
 \end{aligned}$$

- $OR$  approximate  $RR$  if  $P(C | \bar{S})$  and  $P(C | S)$  are small (or if they are nearly equal)



## Rare disease assumption

Exposure	Disease		Total
	Yes	No	
Yes	9	1	10
No	1	999	1000
	10	1000	1010

- Cross-sectional data
- $P(\hat{D}) = 10/1010 \approx .01$
- $\hat{OR} = (9 \times 999)/(1 \times 1) = 8991$
- $\hat{RR} = (9/10)/(1/1000) = 900$
- $D$  is rare in the sample
- $D$  is not rare among the exposed

- $OR = 1$  implies no association
- $OR > 1$  positive association
- $OR < 1$  negative association
- For retrospective CC studies,  $OR$  can be interpreted prospectively
- For diseases that are rare among the cases and controls, the  $OR$  approximates the  $RR$
- Delta method SE for  $\log OR$  is

$$\sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}$$

## Example

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Smoker	Lung cancer		Total
	Cases	Controls	
Yes	688	650	1338
No	21	59	80
	709	709	1418

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- $\hat{OR} = \frac{688 \times 59}{21 \times 650} = 3.0$
- $\hat{SE}_{\log \hat{OR}} = \sqrt{\frac{1}{688} + \frac{1}{650} + \frac{1}{21} + \frac{1}{59}} = .26$
- $CI = \log(3.0) \pm 1.96 \times .26 = [.59, 1.61]$
- The estimated odds of lung cancer for smokers are 3 times that of the odds for non-smokers with an interval of  $[\exp(.59), \exp(1.61)] = [1.80, 5.00]$

## Exact inference for the OR

Smoker	Lung cancer		Total
	Cases	Controls	
Yes	688	650	1338
No	21	59	80
	709	709	1418

- $X$  the number of smokers for the cases
- $Y$  the number of smokers for the controls
- Calculate an exact CI for the odds ratio
- Have to eliminate a nuisance parameter

- $\text{logit}(p) = \log\{p/(1 - p)\}$  is the **log-odds**
- Differences in logits are log-odds *ratios*
- $\text{logit}\{P(\text{Smoker} \mid \text{Case})\} = \delta$ 
  - $P(\text{Smoker} \mid \text{Case}) = e^{\delta}/(1 + e^{\delta})$
- $\text{logit}\{P(\text{Smoker} \mid \text{Control})\} = \delta + \theta$ 
  - $P(\text{Smoker} \mid \text{Control}) = e^{\delta+\theta}/(1 + e^{\delta+\theta})$
- $\theta$  is the log-odds ratio
- $\delta$  is the nuisance parameter

- $X$  is binomial with  $n_1$  trials and success probability  $e^\delta/(1 + e^\delta)$
- $Y$  is binomial with  $n_2$  trials and success probability  $e^{\delta+\theta}/(1 + e^{\delta+\theta})$

$$\begin{aligned}P(X = x) &= \binom{n_1}{x} \left\{ \frac{e^\delta}{1 + e^\delta} \right\}^x \left\{ \frac{1}{1 + e^\delta} \right\}^{n_1 - x} \\&= \binom{n_1}{x} e^{x\delta} \left\{ \frac{1}{1 + e^\delta} \right\}^{n_1}\end{aligned}$$

$$P(X = x) = \binom{n_1}{x} e^{x\delta} \left\{ \frac{1}{1 + e^\delta} \right\}^{n_1}$$

$$P(Y = z - x) = \binom{n_2}{z - x} e^{(z-x)\delta + (z-x)\theta} \left\{ \frac{1}{1 + e^{\delta+\theta}} \right\}^{n_2}$$

$$P(X + Y = z) = \sum_u P(X = u)P(Y = z - u)$$

$$P(X = x \mid X + Y = z) = \frac{P(X = x)P(Y = z - x)}{\sum_u P(X = u)P(Y = z - u)}$$

# Non-central hypergeometric distribution

$$P(X = x \mid X + Y = z; \theta) = \frac{\binom{n_1}{x} \binom{n_2}{z-x} e^{x\theta}}{\sum_u \binom{n_1}{u} \binom{n_2}{z-u} e^{u\theta}}$$

- $\theta$  is the log odds ratio
- This distribution is used to calculate exact hypothesis tests for  $H_0 : \theta = \theta_0$
- Inverting exact tests yields exact confidence intervals for the odds ratio
- Simplifies to the hypergeometric distribution for  $\theta = 0$