	Disease	No Disease	
Exposed	15	85	100
Not	10	90	100
	25	175	

Disease Odds Ratio (DOR)

$$DOR = \frac{Odds \text{ of } D\text{isease given } E\text{xposure}}{Odds \text{ of } D\text{isease given No } E\text{xposure}}$$

$$= \frac{O(D \mid E)}{O(D \mid \bar{E})}$$

$$= \frac{P(D \mid E) \Big/ \left[1 - P(D \mid E)\right]}{P(D \mid \bar{E}) \Big/ \left[1 - P(D \mid \bar{E})\right]}$$

$$= \frac{\frac{15}{100} \Big/ \frac{85}{100}}{\frac{10}{100} \Big/ \frac{90}{100}} = \frac{15 \bullet 90}{10 \bullet 85}$$

	Disease	No Disease	
Exposed	15	85	100
Not	10	90	100
	25	175	

Exposure Odds Ratio (EOR)

$$EOR = \frac{O(E \mid D)}{O(E \mid \bar{D})} = \frac{P(E \mid D) \Big/ \left[1 - P(E \mid D)\right]}{P(E \mid \bar{D}) \Big/ \left[1 - P(E \mid \bar{D})\right]}$$

$$= \frac{\frac{15}{25} \Big/ \frac{10}{25}}{\frac{85}{175} \Big/ \frac{90}{175}} = \frac{15 \bullet 90}{10 \bullet 85}$$

The *Disease* Odds Ratio is equal to the *Exposure* Odds Ratio → the *Odds Ratio* is estimable from either type of study.

When the probability of the disease is small, the Odds Ratio (OR) approximates the Relative Risk (RR).

Sampling Distribution for *ln(OR)*

- $\ln(\hat{OR}) = \ln\left(\frac{a \cdot d}{b \cdot c}\right)$
- Approximately normal with …
- $SE = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

	Case	Control
Exposed	*a*	*b*
Not	*c*	*d*

Reasons for an observed genetic association

- The locus is a functional variant (association is causal)

  Functional variant → Disease

- The locus is in linkage disequilibrium with a functional variant:

  Marker locus $\overset{LD}{\rightarrow}$ Functional variant → Disease

- The association is due to confounding by population stratification

  Marker locus → Population stratification → Functional variant → Disease

Measures of Disease Association – Odds Ratios and Relative Risk

- In epidemiology, association between disease and etiological factors are usually expressed in terms of relative risk measures.

  (Risk of disease in exposed subjects) / (Risk of disease in unexposed subjects)

- In genetic epidemiology, relative risks can be defined for
  - genotypes
  - alleles
  - haplotypes

Genotype Relative Risks (GRRs)

- For a diallelic locus with alleles *A* & *a*, there are three genotypes: *A/A*, *A/a*, *a/a*
- One is typically taken as the reference group (say *a/a*) and GRRs are expressed as

$$GRR_{A/A} = \frac{\text{Risk for A/A geno}}{\text{Risk for a/a geno}} = \phi_{A/A} \quad \& \quad GRR_{A/a} = \frac{\text{Risk for A/A geno}}{\text{Risk for a/a geno}} = \phi_{A/a}$$

- For a rare disease, the RRs can be estimated by odds ratios using case-control data.

	Case	Control
A/A	$D_{A/A}$	$H_{A/A}$
A/a	$D_{A/a}$	$H_{A/a}$
a/a	$D_{a/a}$	$H_{a/a}$

$$OR_{A/A} = \frac{\mathrm{D}_{\mathrm{A/A}} \cdot H_{\mathrm{a/a}}}{H_{\mathrm{A/A}} \cdot \mathrm{D}_{\mathrm{a/a}}}$$

$$OR_{A/a} = \frac{\mathrm{D}_{\mathrm{A/a}} \cdot H_{\mathrm{a/a}}}{H_{\mathrm{A/a}} \cdot \mathrm{D}_{\mathrm{a/a}}}$$

Allelic Relative Risks

- An allelic RR refers to the chromosome-level of analysis, rather than person-level.
- For a diallelic locus we have ϕ_A and ϕ_a. If allele *a* is the reference then $\phi_a = 1$
- They are related to Genotype RRs by a multiplicative model: $\phi_{i/j} = \phi_i \cdot \phi_j$

  → $\phi_{A/A} = (\phi_A)^2$ & $\phi_{A/a} = \phi_A$

- Assuming a rare disease, the multiplicative model, and HW equilibrium in the population, the allelic RR can be estimated by an odds ratio
- The assumptions make it possible to treat chromosomes as independent and analyze the 2x2 allele-level table.

	Case	Control
Allele *A*	*a*	*b*
Allele *a*	*c*	*d*

Example: A SNP in the BRCA1 gene (Pro871Leu)

Subjects

	Case	Control
Leu/Leu	89	56
Leu/Pro	369	250
Pro/Pro	342	266

Chromosomes

	Case	Control
Leu		
Pro		

- Compute the two estimated GRRs (ORs) for the genotype table.
- Fill in the allele table.
- Compute an odds ratio estimate for the *Leu/Leu* genotype based on the multiplicative model.

Dominant & Recessive Models → Different 2x2 Tables

Subjects

	Case	Control
Leu/Leu	89	56
Leu/Pro	369	250
Pro/Pro	342	266

Dominant

	Case	Control
Leu/*	458	306
Pro/Pro	342	266

Recessive

	Case	Control
Leu/Leu	89	56
Pro/*	711	516