JOHNS HOPKINS
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Interaction

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What Is (Biological) Interaction?

- **Interaction** involves two risk factors (and their effect on one disease outcome)
- If the effect of one risk factor is the same within strata defined by the other, then there is NO interaction
- When the effect of one risk factor is different within strata defined by the other, then there is an interaction (biological)

Example of (Biological) Interaction

- Cigarette smoking and radon exposure are two possible risk factors for lung cancer
  - Is there an interaction (biological) between cigarette smoking and radon exposure with regard to lung cancer?
  - If the risk of lung cancer from cigarette smoking is the same among those who were exposed to radon and those who were not exposed to radon, then there is no interaction (biological) between the two risk factors
  - If the risk differs in the two groups, then there is an interaction
- How do we measure or check for the presence/absence of an interaction?

Measures of Interaction

- There are two ways that we measure risk
  1. Ratio of risks
  2. Difference of risks
- (Statistical) interaction can be measured based on the ways that risks are calculated (modeling)
  - When ratio is used, risks are considered to act in a multiplicative way
  - When difference is used, risks are considered to act in an additive way
- The presence of interaction based on measurements is called **statistical interaction,** and inherently it may not reflect the true biological interaction

(Statistical) Interaction or Effect Measure Modification

- (Statistical) interaction occurs when the incidence of disease in the presence of two or more risk factors **differs** from the incidence expected to result from their individual effects

Source: MacMahon, 1972

Implications of Interaction

- **Synergism** increases disease risk beyond expected; persons with one exposure (smoking) are more susceptible to another exposure (radon)
- **Antagonism** decreases disease risk beyond expected; persons with one exposure (smoking) are less susceptible to another (radon)

Hypothetical Data in an Additive Model

Incidence

Factor B	Factor A: –	Factor A: +
–	3	9
+	15	?

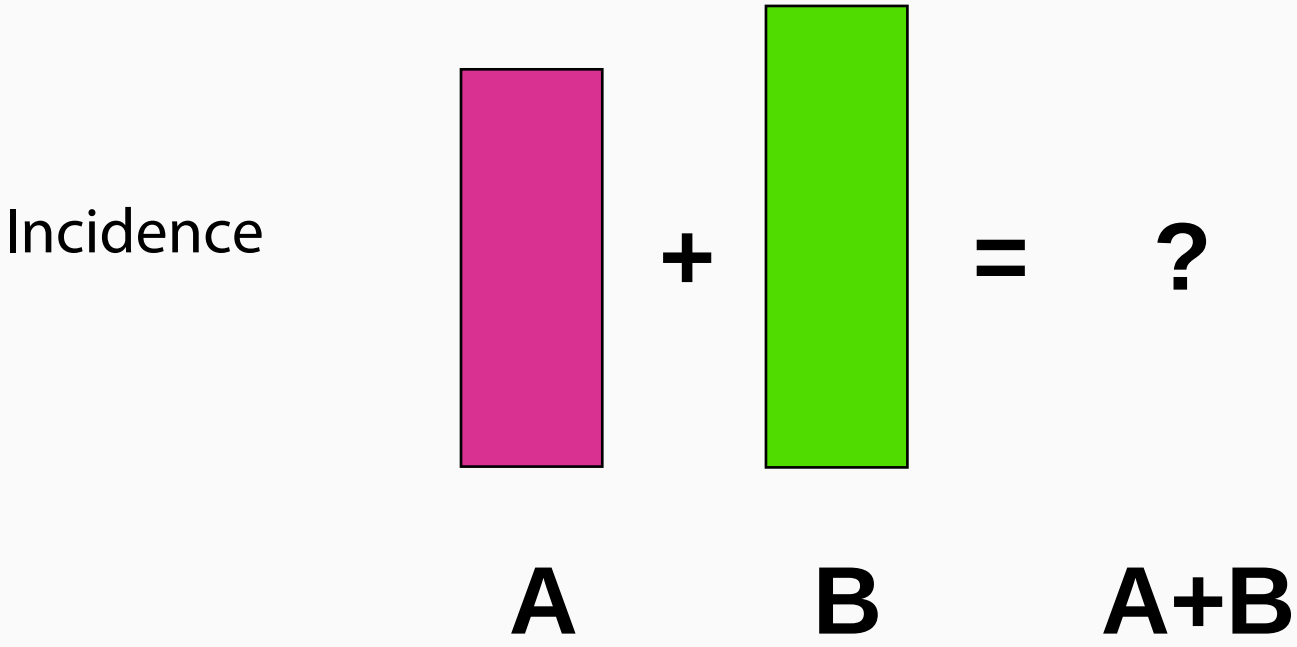
Subtracting Baseline Risk from Each Category

Incidence		Factor A	
		–	+
Factor B	–	3	9
	+	15	?

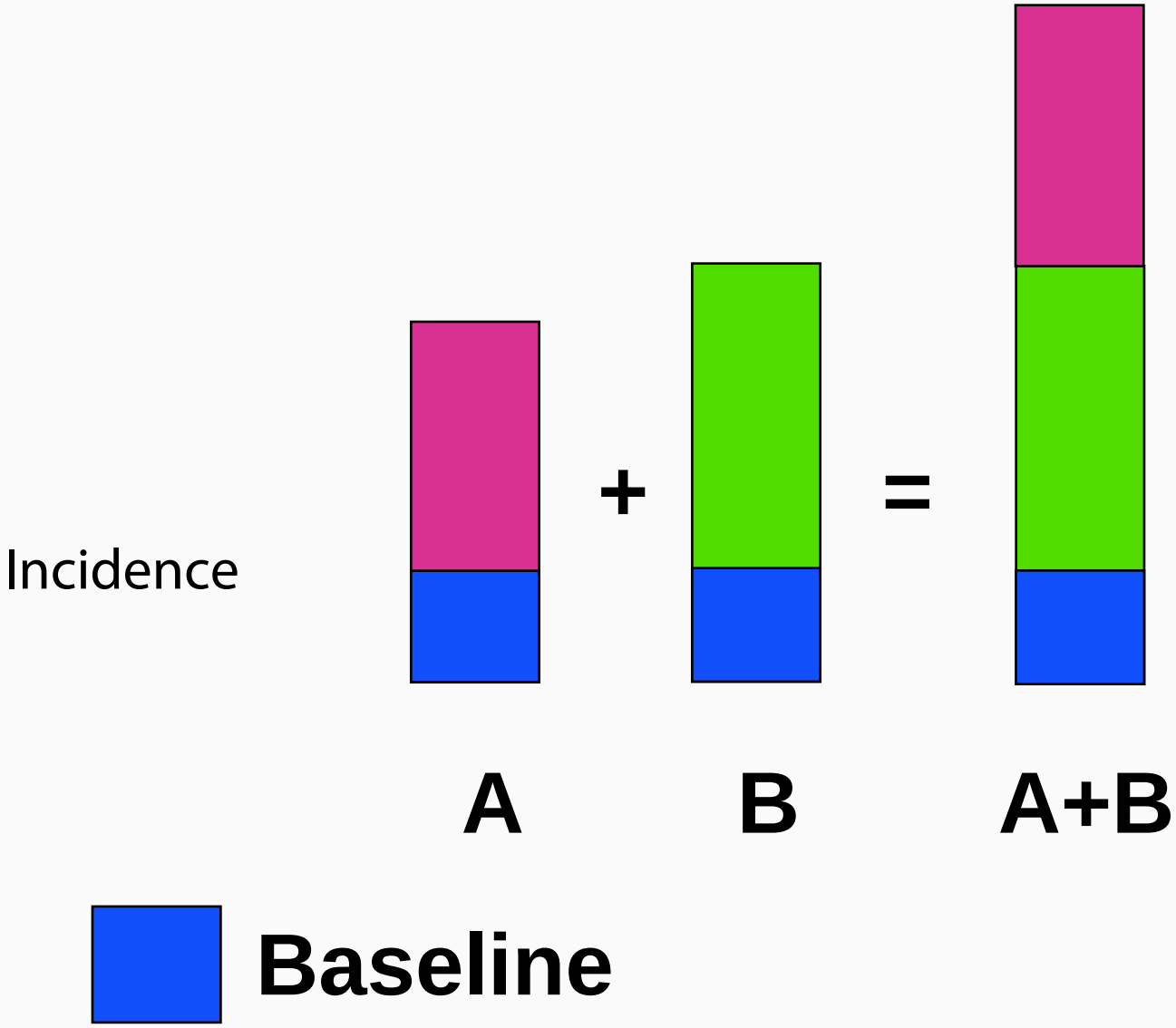
Risk Difference (Attributable Risk)

	Factor A	
	–	+
Factor B –	0	6
Factor B +	12	?

What Is the Expected Incidence of A+B in an Additive Model?



What Is the Expected Incidence of A+B in an Additive Model?



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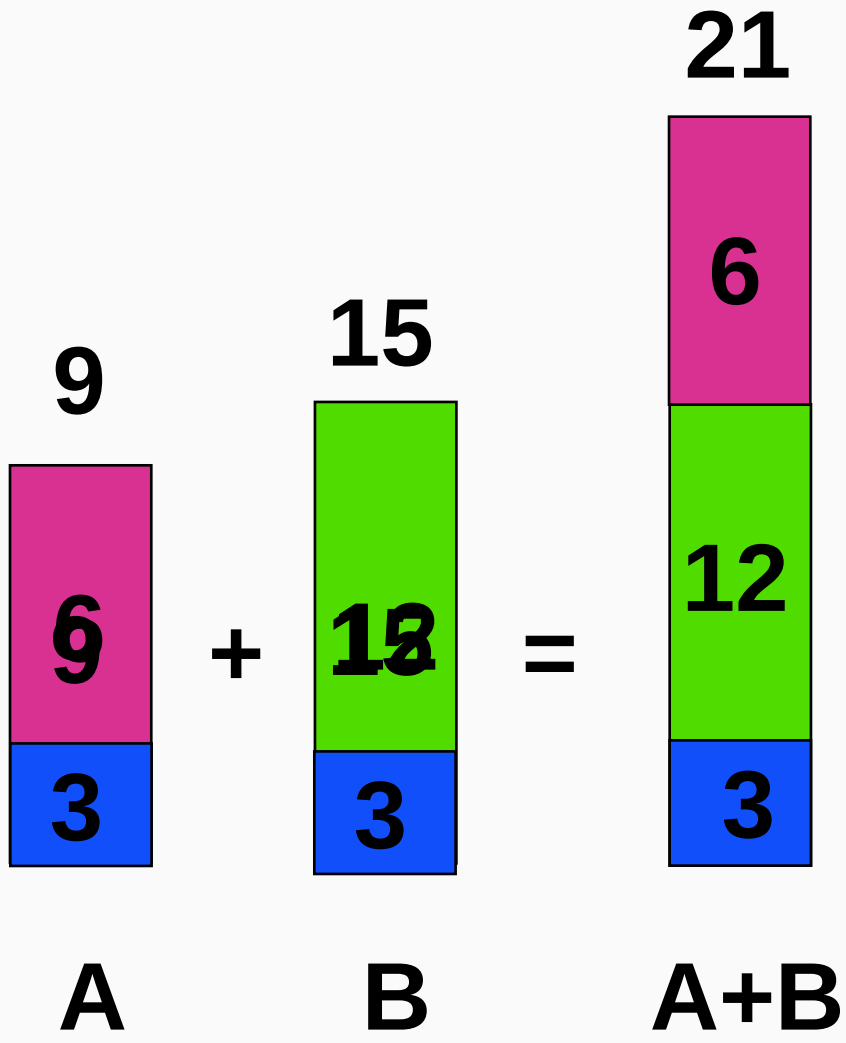

Expected Incidence in an Additive Model

Expected incidence of A and B = Attributable risk of A alone
+ attributable risk of B alone
+ baseline

= Incidence of A alone
+ incidence of B alone
– baseline

Hypothetical Data in an Additive Model

Incidence		Factor A	
		–	+
Factor B	–	**3**	**9**
	+	**15**	**21**

- If there is no interaction between Factors A and B, the incidence of having A and B is expected to be 21
- If the observed incidence in the group having A and B differs from 21, then there is an interaction (statistical) under the additive model

Test for the Presence/Absence of Interaction

Incidence	Factor A: –	Factor A: +
Factor B: –	I_{00}	I_{10}
Factor B: +	I_{01}	I_{11}

- No interaction: $I_{11} - I_{01} = I_{10} - I_{00}$
- Synergistic interaction: $I_{11} - I_{01} > I_{10} - I_{00}$
- Antagonistic interaction: $I_{11} - I_{01} < I_{10} - I_{00}$

Smoking and Radon Exposure In Uranium Miners

Smoking	Radon	Lung Cancer Incidence
No	No	1/1000
No	Yes	5/1000
Yes	No	10/1000
Yes	Yes	50/1000

Smoking and Radon Exposure in Uranium Miners

Incidence		Smoking	
		–	+
Radon	–	**1**	**10**
	+	**5**	**50**

- If there is no interaction between smoking and radon exposure, the incidence of having both is expected to be:

  (5–1)+(10–1) +1 = 14 (or, 5 + 10 –1 = 14)

- But observed incidence is 50/1000; therefore, there is a synergistic interaction in the additive model

Using the Test Equations

Incidence		Smoking	
		–	+
Radon	–	**1**	**10**
	+	**5**	**50**

$I_{11} - I_{01} > I_{10} - I_{00}$

50 - 5 > 10 - 1

Suggests synergistic interaction

Same Hypothetical Data in a Multiplicative Model

Incidence

Factor B	Factor A: –	Factor A: +
–	**3**	**9**
+	**15**	**?**

Calculating Ratio of Risk or Relative Risk in a Multiplicative Model

Incidence		Factor A	
		–	+
Factor B	–	**3**	**9**
	+	**15**	**?**

Dividing by baseline incidence of 3

Relative Risk		Factor A	
		–	+
Factor B	–	**1.0**	**3.0**
	+	**5.0**	**?**

Expected Relative Risk for A+B in a Multiplicative Model

Expected RR for A+B = RR for A only x RR for B only

The Expected RR for Having Factors A and B in a Multiplicative Model

Relative Risk	Factor A	
	–	**+**
Factor B **–**	**1.0**	**3.0**
Factor B **+**	**5.0**	**15.0**

The expected RR for having both A and B = 3.0 x 5.0 = **15.0**

The incidence of having both A and B = baseline I x RR
= 3 x 15.0 = 45

Types of Interaction

- If the observed risk (or incidence) for having both A and B is equal to the expected, then there is **no interaction**
- If the observed risk (or incidence) for having both A and B is greater than the expected risk (or incidence), then there is a **synergistic interaction**
- If the observed risk (or incidence) for having both A and B is less than the expected risk (or incidence), then there is an **antagonistic interaction**

Test for the Presence/Absence of Interaction in a Multiplicative Model

Relative Risk

Factor B	Factor A: −	Factor A: +
−	RR_{00}	RR_{10}
+	RR_{01}	RR_{11}

No interaction : $RR_{11} = RR_{10} \times RR_{01}$

Synergistic Interaction : $RR_{11} > RR_{10} \times RR_{01}$

Antagonistic interaction : $RR_{11} < RR_{10} \times RR_{01}$

Example: Relative Risk of Oral Cancer from Smoking and Alcohol Consumption

Relative Risk		Smoking	
		No	Yes
Alcohol Consumption	No	1.00	1.53
	Yes	1.23	5.71

Rothman K, Keller A. (1972). The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chronic Dis 25:711-716.

Example: Relative Risk of Oral Cancer From Smoking and Alcohol Consumption

Relative Risk		Smoking	
		No	Yes
Alcohol	No	1.00	1.53
	Yes	1.23	5.71

1. The expected RR for smoking and drinking alcohol
   $= 1.53 \times 1.23 = 1.88$
2. Using the test equation to check for interaction
   $5.71 > 1.53 \times 1.23$
   Suggest synergistic interaction in the multiplicative model

Use of Relative Risk in an Additive Model

1. Incidence		Factor A	
		–	+
Factor B	–	**3**	**9**
	+	**15**	**21**

2. Attributable Risk		Factor A	
		–	+
Factor B	–	**0**	**6**
	+	**12**	**18**

3. Relative Risk		Factor A	
		–	+
Factor B	–	**1.0**	**3.0**
	+	**5.0**	**7.0**

Use of Relative Risk in an Additive Model

1. Incidence		Factor A	
		–	+
Factor B	–	3	9
	+	15	21

2. Attributable Risk		Factor A	
		–	+
Factor B	–	0	6
	+	12	18

3. Relative Risk		Factor A	
		–	+
Factor B	–	1.0	3.0
	+	5.0	7.0

No interaction :

(1) $I_{11} - I_{01} = I_{10} - I_{00}$

No interaction :

(2) $RR_{11} - RR_{01} = RR_{10} - RR_{00}$

(3) $RR_{11} - RR_{01} = RR_{10} - 1$

(4) $RR_{11} = RR_{01} + RR_{10} - 1$

Example of Interaction

- Effect of aflatoxin in chronic hepatitis B patient on the development of liver cancer
  - RR of liver cancer from hepatitis B infection alone was 7.3
  - RR of liver cancer from aflatoxin exposure alone was 3.4
  - RR of liver cancer from both was 59.4

Qian GS, Ross RK, Yu MC, et al. (1994). A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. Cancer Epidemiol Biomarkers Prev 3:3-10.

Statistical Interaction versus Biological Interaction

- Is the presence of a biological interaction between two risk factors based on the expectation that the risk factors should interact following an additive or a multiplicative model? Or, should it be based on a special law of biology that is more complex than the measurement tools (modeling) available?
- The answer will likely require a better understanding of the underlying biological mechanisms of disease causation and the causal (or risk) factors
- Since several factors play a role in disease causation, it is important to understand the concept of interaction—especially in individuals with multiple risk factors