Gene-Environment Interaction: Definitions and Study Designs

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Overview

- Definitions of interaction
- Examples of plausible models
- Study designs
- Importance of measurement scale

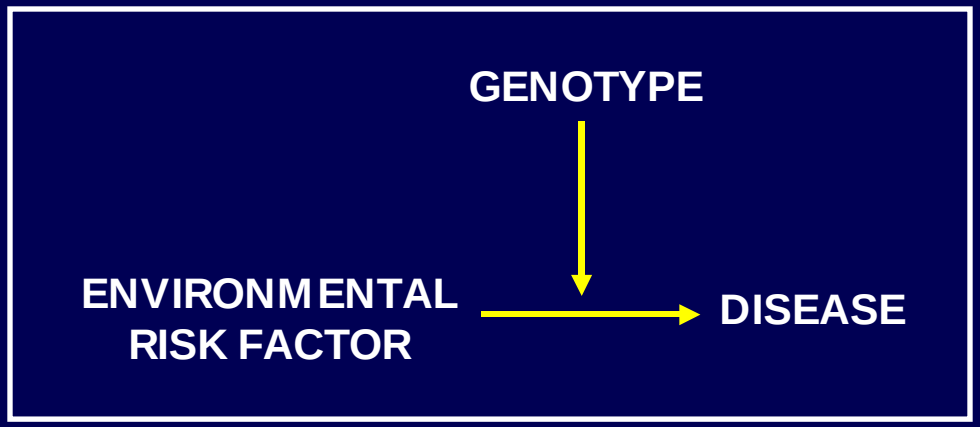
Gene-Environment Interaction

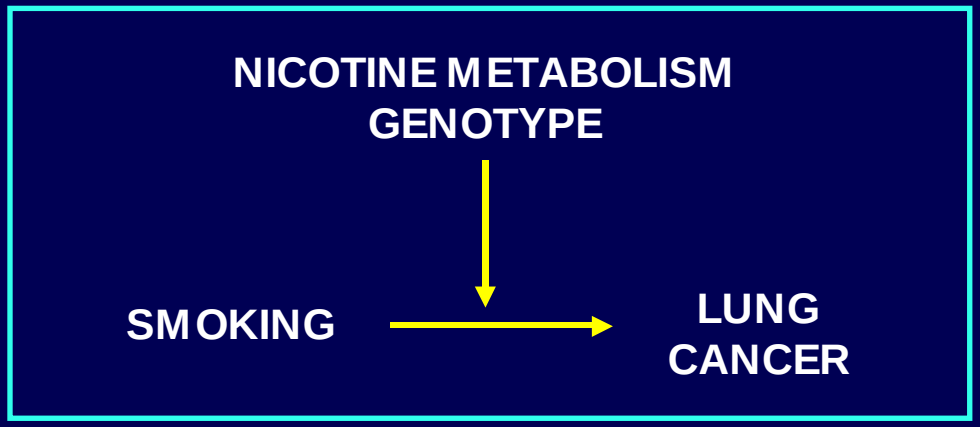
- Definition: A different effect of an environmental factor in people with different genotypes
- Examples: People with different genotypes could differ in…
  - susceptibility to the health effects of exposures such as smoking, drinking, not exercising, etc.
  - responses to life events such as trauma
  - responses to medications (pharmacogenomics)

Statistical Definitions of Interaction

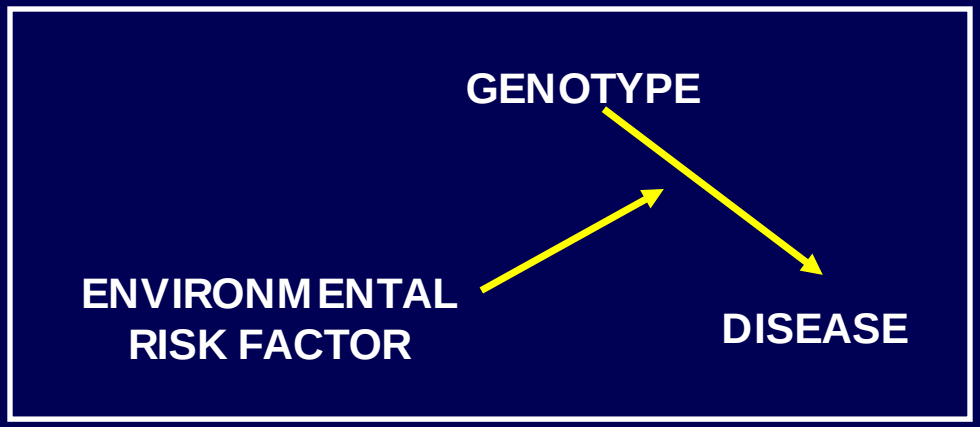
Model	Interpretation
No interaction	The **same effect** of the exposure in people with different genotypes
Synergistic interaction	**Greater effect** of the exposure in people with a genotype of interest than in people with other genotypes
Antagonistic interaction	**Smaller effect** of the exposure in people with a genotype of interest than in people with other genotypes

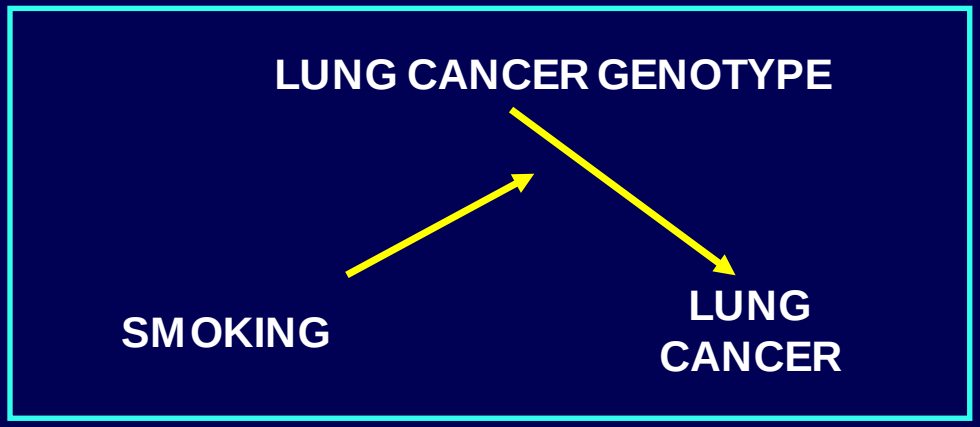
Model 1:
Genotype Exacerbates Effect of Risk Factor



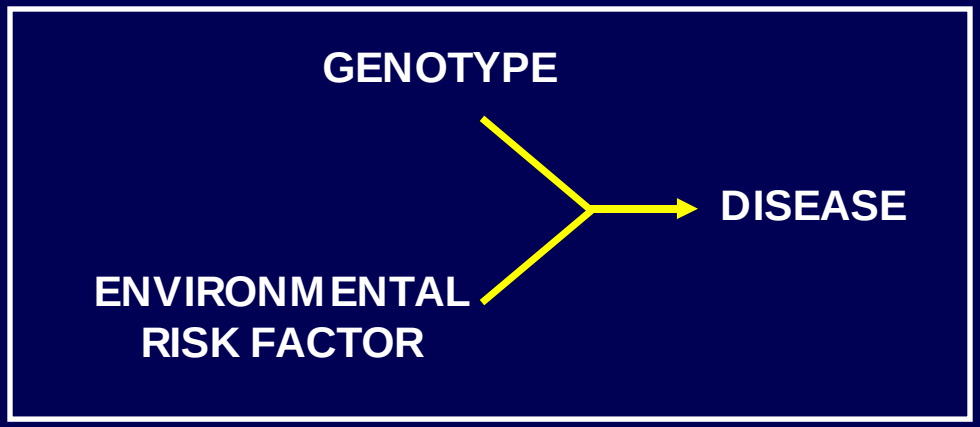


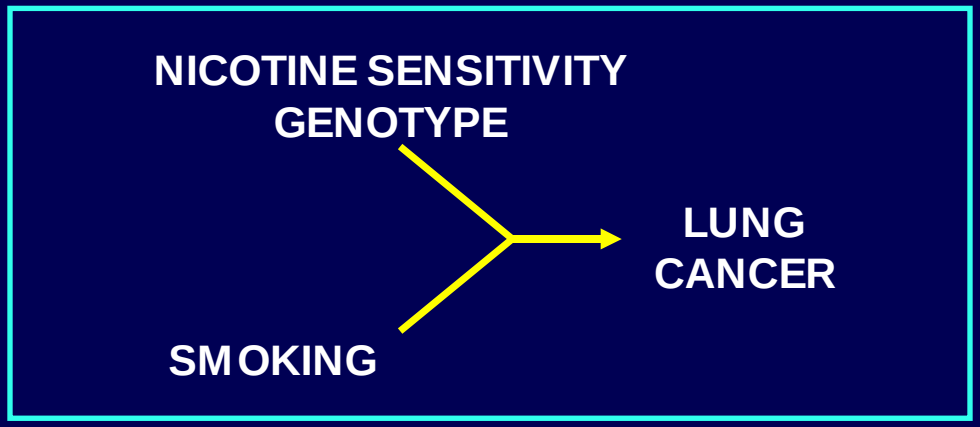
Model 2:
Risk Factor Exacerbates Effect of Genotype



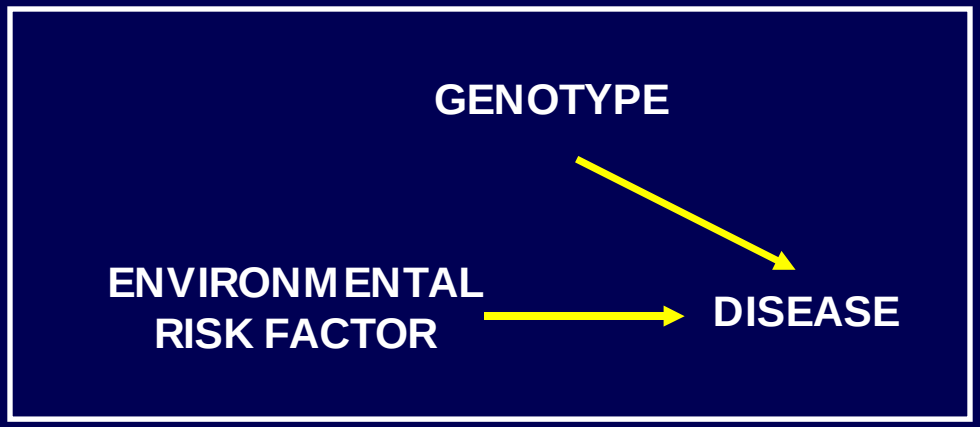


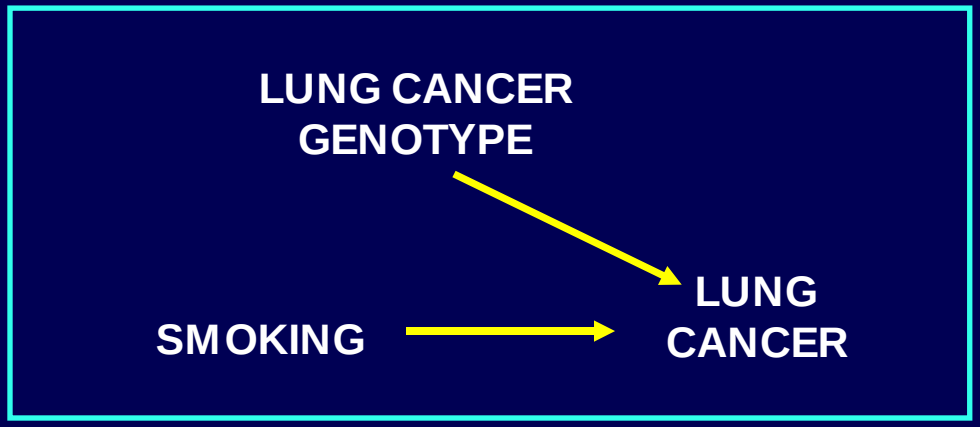
Model 3:
Both Genotype and Risk Factor Required





Model 4:
Combined Effect of Genotype and Exposure Greater than Expected from Individual Effects





Observational Study Designs in Epidemiology

- Prospective Cohort study
  - Individuals who share a characteristic (e.g., birth year, occupation) are followed over time and their disease experience is analyzed for association with exposure(s)
  - Examples: Framingham study, Nurse' s Health Study
- (Retrospective) Case-control study
  - Individuals who have a disease (case) are compared with those who do not (controls), in terms of their previous exposures

Effect Measures

COHORT STUDY:	Environmental Factor Present	Environmental Factor Absent
Affected	a	b
Unaffected	c	d
Risk	a/(a+c)	b/(b+d)
Relative risk	$\frac{a/(a+c)}{b/(b+d)}$	
Risk difference	a/(a+c) – b/(b+d)	

CASE-CONTROL STUDY:	Environmental Factor Present	Environmental Factor Absent
Cases	a	b
Controls	c	d
Odds ratio	$\frac{ad}{bc}$	

Studies of Genes and Environment: 4 groups defined by genotype and exposure

COHORT STUDY:	G+ E+	G+ E-	G- E+	G- E-
Affected	a	b	e	f
Unaffected	c	d	g	h
Risk	a/(a+c)	b/(b+d)	e/(e+g)	f/(f+h)
Relative risk	$RR_{G+} = \frac{a/(a+c)}{b/(b+d)}$		$RR_{G-} = \frac{e/(e+g)}{f/(f+h)}$	
Risk difference	$RD_{G+} = a/(a+c) - b/(b+d)$		$RD_{G-} = e/(e+g) - f/(f+h)$	

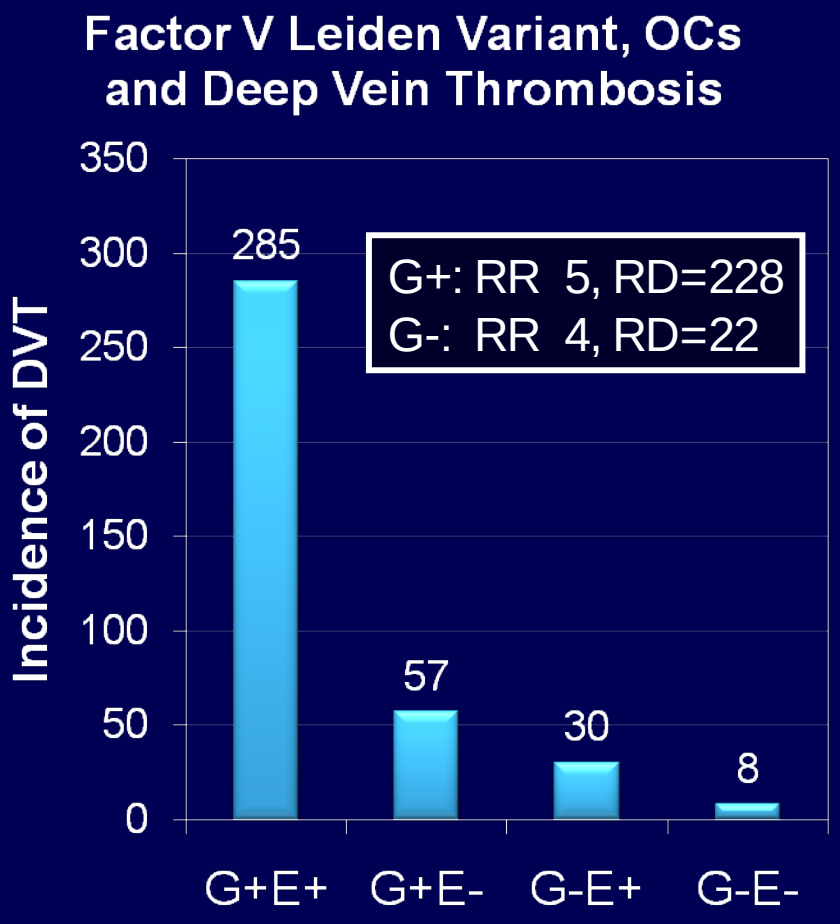
Test for interaction: Is the effect of the exposure *the same* in people with and without the high-risk genotype?

Multiplicative scale: No interaction implies $RR_{G+} = RR_{G-}$

Additive scale: No interaction implies $RD_{G+} = RD_{G-}$

Importance of Measurement Scale

- Statistical tests for interaction depend on the measurement scale (additive or multiplicative)
- Different measurement scales lead to different conclusions (and different public health recommendations!)
- The same data can be made to fit more than one model
- Use of a purely statistical approach is inadequate -- a different approach more closely tied to biology is needed!



Vandenbroucke et al., 1994

Concepts of Interaction in Epidemiology

- A disease may result from many alternative “ sufficient causes” (each possibly involving multiple “ component causes”)
- Two factors “ interact” (in a biological sense) if they are components of the same sufficient cause
- Analysis using potential outcomes models: If two factors are part of different sufficient causes, their combined effects on risk will tend to be additive
- This implies interaction should be measured on an additive scale

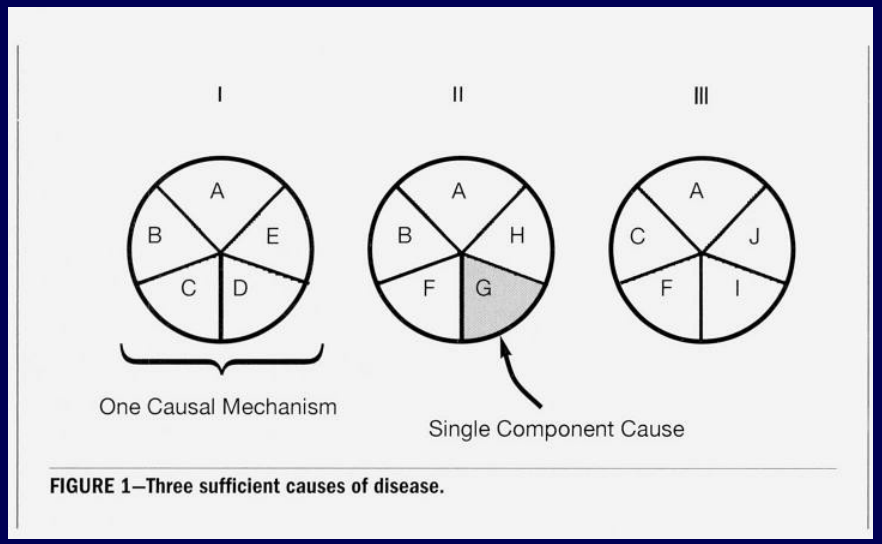


FIGURE 1—Three sufficient causes of disease.

Rothman KJ, Greenland S. Am J Public Health. 2005;95 Suppl 1:S144-50.

Summary

- Studies of interaction need to consider the scale of measurement
- Additive scale more consistent with biological models
- Methods development needed to make tests on additive scale more accessible
- Large sample sizes needed, so collaboration is essential