Effect measure modification

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Outline

- Definition and terminology
- Effect modification vs. confounding
- Scale dependence
- Assessment of effect measure modification
- Examples

Definition

"Effect (measure) modification occurs when the association between an exposure and an outcome is modified by some other factor"

Practical definition

"In practice, effect modification occurs when the combined risk mediated by two factors is different than the sum of the two factors assessed independently"

So what?

- Effect modification occurs when the association between the exposure and outcome is modified by a third variable

Lung cancer risk / 1000 person years

	Asbestos	No asbestos
Smoker	50	10
Non-smoker	8	1

So what?

Lung cancer risk / 1000 person years

	Asbestos	No asbestos
Smoker	50	10
Non-smoker	8	1
Risk difference	42	9
Relative risk	6.1	10

Biostatistician's interpretation (1)*

- The relative risk of lung cancer in relation to smoking is 10 in the general population, but 6.1 among asbestos workers
- There is negative effect modification (the effect of smoking is lower in asbestos workers)

Lung cancer risk / 1000 person years

	Asbestos	No asbestos
Smoker	50	10
Non-smoker	8	1
Risk difference	42	9
Relative risk	6.1	10

*Example borrowed from Dr Neil Pearce, Centre for Public Health Research, Massey University, NZ

Biostatistician's interpretation (2)*

- The risk difference of lung cancer in relation to smoking is 42 among asbestos workers, but only 9 in the general population
- There is positive effect modification (the effect of smoking is higher in asbestos workers)

Lung cancer risk / 1000 person years

	Asbestos	No asbestos
Smoker	50	10
Non-smoker	8	1
Risk difference	42	9
Relative risk	6.1	10

*Example borrowed from Dr Neil Pearce, Centre for Public Health Research, Massey University, NZ

Clinician's interpretation*

- The possible gain of smoking cessation is greater in asbestos workers
- There is positive effect modification (the gain for the individual patient is greater in asbestos workers)

Lung cancer risk / 1000 person years

	Asbestos	No asbestos
Smoker	50	10
Non-smoker	8	1
Risk difference	42	9
Relative risk	6.1	10

*Example borrowed from Dr Neil Pearce, Centre for Public Health Research, Massey University, NZ

Terminology

- Synonyms:
  - Heterogeneity of effect – "the effect of the exposure is heterogeneous"
  - Interaction – "the exposure and the modifying factor interact"
- Homogeneity of effect – the effect of the exposure is homogenous, thus there is absence of effect measure modification

Synergism

- On a relative scale, synergism occurs when the relative risk among individuals with both the exposure and the interaction factor is greater than the sum of their independent effects
- Synergism is also referred to as "positive interaction"

Antagonism

- Conversely (again on a relative scale), antagonism occurs when the relative risk among individuals with both the exposure and the interaction factor is smaller than the sum of their independent effects
- Antagonism is also referred to as "negative interaction"

Statistical interaction

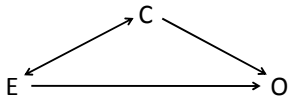
- Statistical interaction (which is really the same as effect modification), is the mode of which we test for effect modification in statistics
- On the most basic (and intuitive) level, interaction is assessed through stratification:
  - what is the effect of the exposure of interest on the risk of the outcome in relation to the third factor?
- If there is evidence of interaction, the emphasis in presentation should be on the stratified risk estimates
  - The combined effect may still be useful as an average

Statistical interaction, cont.

- In regression models, we test for effect modification by entering an interaction term – testing for the combined effect of the variables in question – still analyzing also the main effects
  - Statistical interaction can be 2-way (two variables), 3-way (three variables), etc.
- Unfortunately, tests for heterogeneity (interaction tests) are notoriously low-powered, so we often have to rely on "gut feeling"

Effect modification and confounding

- To repeat, confounding occurs when we have a mixing of effects between the exposure of interest and a third variable
  - We define a confounder as a variable which is associated with the exposure of interest and at the same time is also an independent risk factor for the outcome of interest



Effect modification and confounding

- Although confounding and effect modification both involve a third factor affecting the association between the exposure and outcome, they are fundamentally different
- For practical reasons, it is very important to keep in mind that:
  - Effect modification = good
  - Confounding = bad

Effect modification and confounding

- Effect modification is something we want to study, and report:
  - Effect modification often reflects a deeper effect which is integral in biologic systems
  - Presence of strong effect modification, may in fact suggest interesting biologic mechanisms
  - *Presence of effect modification may also be an effect of scale dependence**
- At the same time, we want to avoid or, whenever possible, eliminate confounding

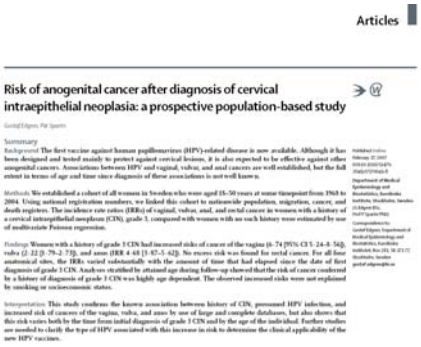
Effect modification and confounding

- In the assessment of the relationship between an exposure (smoking) and an outcome (lung cancer), a third factor may be:
  - Neither an effect modifier nor a confounder
    - E.g. coffee drinking!
  - Both an effect modifier and a confounder
    - E.g. asbestos exposure (maybe…)
  - An effect modifier, but not a confounder
    - E.g. polymorphic Alfa1-antitrypsin gene
  - Not an effect modifier, but a confounder
    - E.g. recreational use of cannabis

Scale dependence

- As shown in the example, effect modification is scale dependent, meaning that:
  - If effect modification does not exist on an absolute scale, it is by definition present on the relative scale
  - Conversely, if effect modification does not exist on a relative scale, it is by definition present on the absolute scale
- It is therefore necessary to be scale-specific when describing effect modification

Evaluation of effect modification



Articles

Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study

Gustaf Edgren, Pär Sparén

Summary

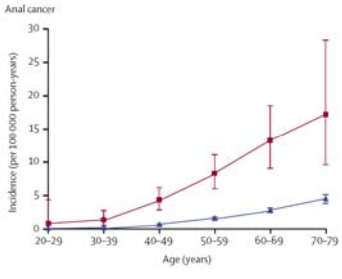
Background The first vaccine against human papillomavirus (HPV)-related disease is now available. Although it has been designed and tested mainly to protect against cervical lesions, it is also expected to be effective against other anogenital cancers. Associations between HPV and vaginal, vulvar, and anal cancers are well established, but the full extent in terms of age and time since diagnosis of these associations is not well known.

Methods We established a cohort of all women in Sweden who were aged 15–50 years at some timepoint from 1968 to 2004. Using national registration numbers, we linked this cohort to nationwide population, migration, cancer, and death registers. The incidence rate ratios (IRRs) of vaginal, vulvar, anal, and rectal cancer in women with a history of a cervical intraepithelial neoplasia (CIN), grade 3, compared with women with no such history were estimated by use of multivariate Poisson regression.

Findings Women with a history of grade 3 CIN had increased risks of cancer of the vagina (6·74 [95% CI 5·24–8·56]), vulva (2·22 [1·79–2·73]), and anus (IRR 4·48 [3·47–5·62]). No excess risk was found for rectal cancer. For all four anatomical sites, the IRRs varied substantially with the amount of time that had elapsed since the date of first diagnosis of grade 3 CIN. Analyses stratified by attained age during follow-up showed that the risk of cancer conferred by a history of diagnosis of grade 3 CIN was highly age dependent. The observed increased risks were not explained by smoking or socioeconomic status.

Interpretation This study confirms the known association between history of CIN, presumed HPV infection, and increased risk of cancers of the vagina, vulva, and anus by use of large and complete databases, but also shows that this risk varies both by the time from initial diagnosis of grade 3 CIN and by the age of the individual. Further studies are needed to clarify the type of HPV associated with this increase in risk to determine the clinical applicability of the new HPV vaccines.

Evaluation of effect modification



CIN3 history	0·79	1·35	4·32	8·30	13·21	17·20
No CIN3 history	0·03	0·17	0·66	1·58	2·79	4·48
Risk difference	0·76	1·18	3·66	6·72	10·42	12·72

Evaluation of effect modification

- Although we've concluded that confounding effect modification are fundamentally different, the basic analysis is the same
  - First conduct crude analysis
  - If you suspect effect modification, start with straightforward stratification
    - What is the effect of the exposure on the risk of the outcome, in strata of the effect modifier?
    - Are the stratified risk estimates different (i.e. do we have evidence of effect modification)?

Evaluation of effect modification

- We start by calculating the crude IRR:

$$IRR = \frac{131/2{,}193{,}409}{857/88{,}927{,}325} = 6.2$$

- We can also calculate the crude incidence rate difference:

$$IRD = 131/2{,}193{,}409 - 857/88{,}927{,}325$$

- IRD=5.0/100,000 p-y

Prior CIN3 diagnosis	Anal cancer cases	Person-time
+	131	2,193,409
-	857	88,927,325

Evaluation of effect modification

- As we are suspecting an age interaction, we then proceed with stratified analyses:

Age	Prior CIN3 diagnosis	Anal cancer cases	Person-time	IRR	IRD
18-49	+	37	1,317,476	11.0	2.6
	-	156	60,925,635		
50-79	+	94	875,933	4.3	8.2
	-	701	28,001,690		

Evaluation of effect modification

- Comparison of risk estimates:

$IRR_{<50}=11.0 \neq IRR_{\geq 50}=4.3$

$IRD_{<50}=2.6 \neq IRD_{\geq 50}=8.2$

Evaluation of effect modification

- So, on a relative scale, old age negatively modifies the association between a history of a CIN3 diagnosis and the risk of anal cancer
- Conversely, on an absolute scale, old age positively modifies the association between a history of a CIN3 diagnosis and the risk of anal cancer
  - Thus, age modifies the association of interest on both scales, albeit in different directions

Evaluation of effect modification

- Which is the correct risk estimate to present?

$IRR_{Total}=6.2 \neq IRR_{<50}=11.0 \neq IRR_{\geq 50}=4.3$

Summary – effect modification

- Effect modification occurs when the combined risk of two factors is different than the sum of the effects of these two factors assessed independently
- While bearing some similarity, effect modification is fundamentally different from confounding:
  - Effect modification is a natural phenomenon we want to investigate further and report
  - Confounding, however, is a nuisance that we want to avoid or adjust for
- Effect modification is scale-dependent