Introduction to study design: cohort studies

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Outline

- Introduction
- Descriptive studies
- Cohort studies
- Summary

Study design – two principal approaches

Experiments	**Observational studies**
”Change the state of nature and observe the effects”	”Observe nature as it is”
Examples: - Randomized studies - Cross-over studies - Etc.	Examples: - Cohort studies - Case-control studies - Cross sectional studies

Example – scurvy

”A condition caused by insufficient intake of vitamin C leading to (among other things) bleeding various mucous membranes and is invariably fatal if left untreated.”

Example – scurvy

- Known since the middle ages
- Previously the principal limiting factor in marine travel
  - 80% of the crew during Magellan’s circumnavigation died from scurvy
- The successful treatment of scurvy with citrus fruits was only formally proved by James Lind in 1747 (published in 1753)

Scurvy and vitamin C

- James Lind observed that during Lord Anson’s circumnavigation, 1400 of 1900 men in the crew died of scurvy (sic!)
- He started by doing a systematic review of the evidence
- Then he proceeded with doing a controlled study (possibly the first), where he tested 6 different treatments in 12 diseased sailors

Scurvy and vitamin C

- All 12 sailors got the same food and lived together, and in addition each day…
  - 2 received one pint of sea water
  - 2 received 25 drops of *elixir vitriol* (!)
  - 2 received one quart of cider
  - 2 received 2 spoons of vinegar
  - 2 received 2 oranges and 1 lemon
  - 2 received a spicy mix of nutmeg, garlic and a few other ingredients

Scurvy and vitamin C

”The consequence was that the most sudden and visible good effect were perceived from the use of oranges and lemons”

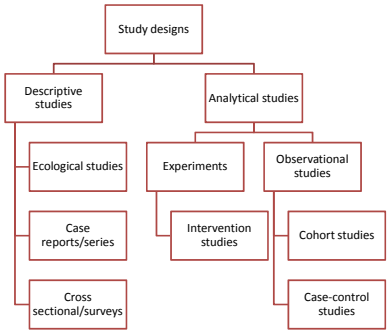
Scurvy and vitamin C – conclusion?

- Insightfully, Lind concluded that the study was too small and needed to be repeated by other scientists…

Rationale for observational studies

- The medical experiment is fairly clear cut (and will be dealt with in detail this afternoon), but what do we do when the exposure can't ethically be assigned?
  - Previous abortion and risk of breast cancer?
  - Smoking and lung cancer risk?
  - etc.
- Thus, we often have to resort to observing what happens in nature…

Overview – study design

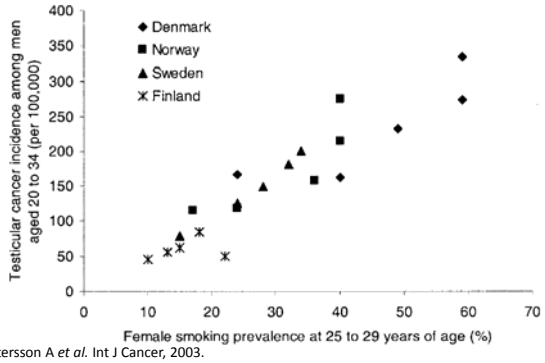


DESCRIPTIVE STUDIES

Ecological studies

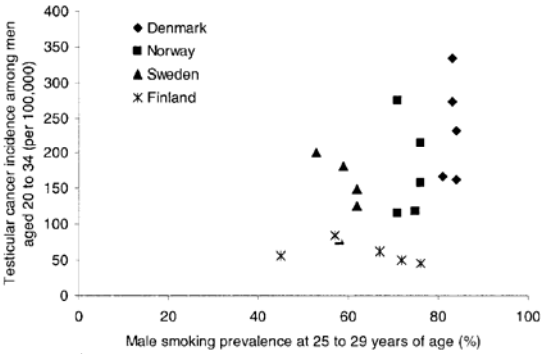
- The most basic type of descriptive study
  - Based on addressing correlations between variables measures on group level
    - E.g. country level, hospital level, etc.
  - No access to individual data, nor to data on important confounders
  - Often considered the weakest in the ”study design hierarchy”
  - Usually used for hypothesis generation

Ecological study – example



Pettersson A *et al.* Int J Cancer, 2003.

Ecological study – example



Pettersson A *et al.* Int J Cancer, 2003.

Striking data – true effect?

- The ecological data is striking…
- The same researchers therefore designed and conducted a nested case-control study (an analytical study) using linkage data from the Swedish medical birth and cancer registers

TABLE II – ADJUSTED ODDS RATIOS OF GERM-CELL TESTICULAR CANCER FOR MATERNAL SMOKING DURING PREGNANCY BY HISTOLOGICAL SUBGROUP

Characteristic	Seminoma			Nonseminoma		
	Cases	Controls	Adjusted OR[1,2]	Cases	Controls	Adjusted OR[1,2]
Maternal smoking (cigarettes/day)						
None	34 (77)[3]	69 (59)	1.00	77 (52)	204 (54)	1.00
<10	4 (9)	24 (21)	0.29 [0.09–0.99][4]	30 (20)	78 (21)	1.00 [0.60–1.66]
>10	6 (14)	23 (20)	0.49 [0.17–1.43]	41 (28)	96 (25)	1.18 [0.73–1.91]

[1]OR, odds ratio.–[2]ORs are adjusted for age, place of birth, maternal age at delivery, birth order and gestational duration.–[3]Values in parentheses indicate percentages.–[4]Values in square brackets indicate 95% confidence intervals.

Pettersson A *et al.* Int J Cancer, 2007.

"Correlation does not imply causation"

Case reports/series – example

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2004 VOL. 350 NO. 4

Discordant Sexual Identity in Some Genetic Males with Cloacal Exstrophy Assigned to Female Sex at Birth

William G. Reiner, M.D., and John P. Gearhart, M.D.

ABSTRACT

BACKGROUND

Cloacal exstrophy is a rare, complex defect of the entire pelvis and its contents that occurs during embryogenesis and is associated with severe phallic inadequacy or phallic absence in genetic males. For about 25 years, neonatal assignment to female sex has been advocated for affected males to overcome the issue of phallic inadequacy, but data on outcome remain sparse.

Reiner WG *et al.* N Engl J Med, 2004.

Case reports/series – example

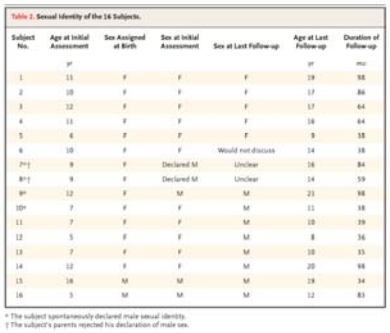


Table 2. Sexual Identity of the 16 Subjects.

Subject No.	Age at Initial Assessment	Sex Assigned at Birth	Sex at Initial Assessment	Sex at Last Follow-up	Age at Last Follow-up	Duration of Follow-up
	yr				yr	mo
1	11	F	F	F	19	98
2	10	F	F	F	17	86
3	12	F	F	F	17	64
4	11	F	F	F	16	64
5	6	F	F	F	9	38
6	10	F	F	Would not discuss	14	38
7*†	9	F	Declared M	Unclear	16	84
8*†	9	F	Declared M	Unclear	14	59
9*	12	F	M	M	21	98
10*	7	F	F	M	11	38
11	7	F	F	M	10	39
12	5	F	F	M	8	36
13	7	F	F	M	10	35
14	12	F	F	M	20	98
15	16	M	M	M	19	34
16	5	M	M	M	12	83

* The subject spontaneously declared male sexual identity.
† The subject's parents rejected his declaration of male sex.

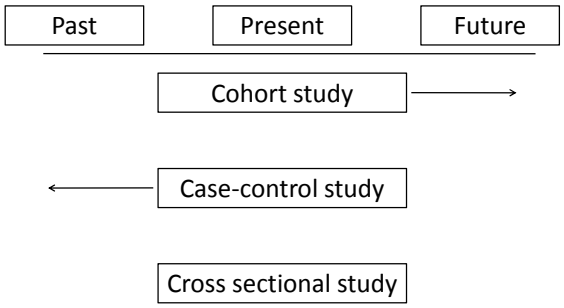
Reiner WG *et al.* N Engl J Med, 2004.

Case reports/series

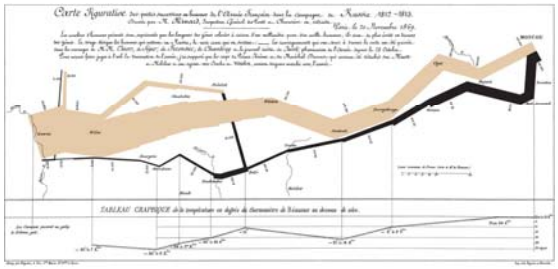
- Reports of individual or series of cases suggesting a certain causal mechanism
- Naturally only suggestive evidence and is primarily hypothesis generating
- For the excruciatingly rare conditions, sometimes the only available evidence…

ANALYTICAL STUDIES

Analytical studies, schematic



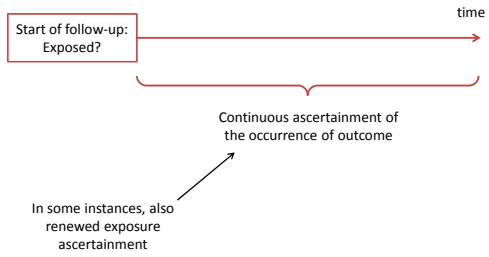
Cohort studies – mother of all studies



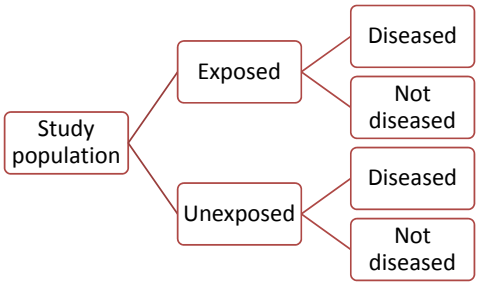
Cohort studies

- Cohort studies = prospective/longitudinal studies
- A group of people followed over a period of time for an outcome (in medicine, usually a disease or death)
- The risk of this outcome is correlated to an exposure (or many exposures), which is typically a treatment or a suspected risk factor

Cohort studies – schematic



Cohort studies – schematic



Cohort studies – different types

- Prospective vs. retrospective cohorts
- Closed vs. open cohorts
  - Static populations (e.g. patients entered into a clinical trial)
  - Dynamic populations (e.g. the population of Singapore)
- Internal vs. external comparison
  - Internal – with comparison between individuals of different exposure levels within the cohort
  - External – with comparison to some suitable background population (remember: SIRs/SMRs)

Closed cohorts

- The "traditional" cohort design, with individuals entered into the study at one defining time point
  - Sometimes due to participation in a defining event (e.g. people in Hiroshima at the time of the bombing in 1945). Other examples are clinical trial participants
  - No new participant can enter the cohort and no participants can leave
  - Equal time at risk for all participants

Closed cohorts (2)

- The number of study participants is constant (or can only decrease)
- Possible to directly calculate
  - Cumulative incidence (ratios/differences) – unique for this study design
  - Incidence rate (ratios/differences)
  - etc.

Closed cohort – example


The New England
Journal of Medicine

VOLUME 347 JULY 11, 2002 NUMBER 2

A CONTROLLED TRIAL OF ARTHROSCOPIC SURGERY FOR OSTEOARTHRITIS OF THE KNEE

J. Bruce Moseley, M.D., Kimberly O'Malley, Ph.D., Nancy J. Petersen, Ph.D., Terri J. Menke, Ph.D., Baruch A. Brody, Ph.D., David H. Kuykendall, Ph.D., John C. Hollingsworth, Dr.P.H., Carol M. Ashton, M.D., M.P.H., and Nelda P. Wray, M.D., M.P.H.

Moseley JB *et al.* N Engl J Med, 2002.

Open cohort

- Participation defined by other means
  - Often just the state of being a part of the study in question (and, naturally, being monitored for the outcome)
- Date of entry and exit from the study is individually defined
  - Time at risk is thus individual
- The size of the study population is thus not constant

Open cohort (2)

- Due to the individual data, cumulative incidence cannot be directly calculated (nor CIRs)
- Therefore, in open cohort studies, researchers can only calculate rate-based data:
  - Incidence rates, and
  - Incidence rate ratios or incidence rate differences
  - And variants thereof (such as hazard ratios)
- (However, cumulative incidence can be *estimated*)

Open cohort studies – example

Cancer Incidence in Blood Transfusion Recipients

Henrik Hjalgrim, Gustaf Edgren, Klaus Rostgaard, Marie Reilly, Trung Nam Tran, Kjell Einar Titlestad, Agneta Shanwell, Casper Jersild, Johanna Adami, Agneta Wikman, Gloria Gridley, Louise Wideroff, Olof Nyrén, Mads Melbye

Background Blood transfusions may influence the recipients' cancer risks both through transmission of biologic agents and by modulation of the immune system. However, cancer occurrence in transfusion recipients remains poorly characterized.

Methods We used computerized files from Scandinavian blood banks to identify a cohort of 888843 cancer-free recipients transfused after 1968. The recipients were followed from first registered transfusion until the date of death, emigration, cancer diagnosis, or December 31, 2002, whichever came first. Relative risks were expressed as ratios of the observed to the expected numbers of cancers, that is, standardized incidence ratios (SIRs), using incidence rates for the general Danish and Swedish populations as a reference. All statistical tests were two-sided.

Results During 5652918 person-years of follow-up, 80990 cancers occurred in the transfusion recipients, corresponding to a SIR of 1.45 (95% confidence interval [CI] = 1.44 to 1.46). The SIR for cancer overall decreased from 5.36 (95% CI = 5.29 to 5.43) during the first 6 months after transfusion to 1.10 or less for follow-up periods more than 2 years after the transfusion. However, the standardized incidence ratios for cancers of the tongue, mouth, pharynx, esophagus, liver, and respiratory and urinary tracts and for squamous cell skin carcinoma remained elevated beyond 10 years after the transfusion.

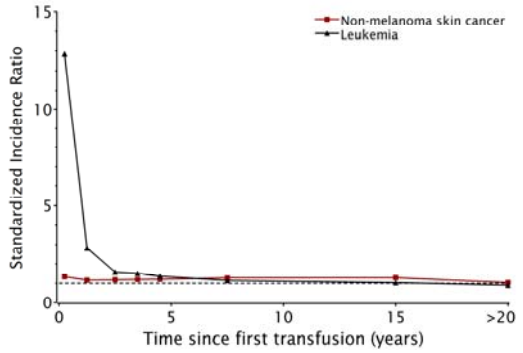
Conclusions The marked increase in cancer risk shortly after a blood transfusion may reflect the presence of undiagnosed occult cancers with symptoms that necessitated the blood transfusion. The continued increased risk of tobacco- and alcohol-related cancers suggests that lifestyle and other risk factors related to conditions prompting transfusion rather than transfusion-related exposures per se are important to the observed cancer occurrence in the recipients.

Hjalgrim H *et al.* J Natl Can Inst, 2007.

Open cohort studies – example

- All transfusion recipients in Sweden and Denmark from 1968 and onwards
- Exposure measured using transfusion registers
- Subjects followed from date of first transfusion until date of death, emigration, first cancer diagnosis, or end of follow-up
- By convention, an example of a retrospective cohort study…

Open cohort studies – example



Hjalgrim H *et al.* J Natl Can Inst, 2007.

Prospective vs. retrospective

- Cohort studies can be conducted using data collective prospectively
  - Typical example, investigator initiated studies such as the Framingham heart study
- or, with data recorded for other reasons and recycled for the purpose of new research questions:
  - Often register based studies

Prospective vs. retrospective (2)

- The primary distinction is whether the investigator initiates collection of these data (prospective) or uses previously collected data (retrospective)
- Thus, the distinction between prospective and retrospective cohort studies is often arbitrary
- However, some caution is warranted with regards to selection bias (Thursday!)

Prospective cohort studies

- Exposure is collected by the investigator at the start of the study period
  - The natural advantage is that the investigator can guide what data about exposure and outcome is collected
  - However, as a consequence, truly prospective cohort studies are very expensive and time consuming

Retrospective cohort studies

- Based on the availability of data collected for other reasons (e.g. transfusion registers), cohort studies can also be conducted using retrospective data
  - These have the advantages of being cheaper, more efficient and less time-consuming
  - Naturally, they retrospective studies suffer with the quality of the data collected and since these data cannot be extended, the investigator is locked to whatever was collected

Internal vs. external comparison

- In any cohort study, comparisons can be made between different exposure groups (internal comparison), or between the study population as a whole and the "background" population (external comparison)
- In external comparisons, researchers typically calculate incidence rate ratios that are standardized to the age-, sex- and calendar period structure of the background population (i.e. the general population) – thus adjusting for these variables

Notes on exposure

- Subjects can be selected from special exposure groups (usually for efficiency), examples:
  - Occupation groups (e.g. Asbestos workers)
  - Subjects from a rare event (e.g. Tsunami cohort)
  - Patients
- Exposure groups always selected with principle of the counterfactual ideal in mind*

Notes on outcome

- As with exposure information, the outcome can come from many different sources:
  - Self report
  - National (or regional) census data
  - Registers (often preferential, if the prerequisites exist)
  - Hospital case records
  - etc.

Cohort studies – pros

1. Once launched, in a cohort study, it is possible to study a multitude of outcomes
2. Excellent for rare exposures (e.g. miners working in a Beryllium mine)
3. Certain (more or less) time sequence of exposure and outcome
4. With multiple exposure measurements, possible to study change in exposure
5. Possible to directly measure incidence

Cohort studies – cons

1. Unless data is already collected (i.e. retrospective), cohort studies are very expensive and time-consuming
2. Usually not suitable for rare outcomes (e.g. 1,000,000 subjects need to be followed for 5-10 years for 20 cases of pheochromocytoma to accrue)
3. For retrospective studies, inflexibly locked to the pre-collected data
4. As with all observational studies, uncontrollable confounding is an ever present threat

Summary

- Study designs can typically be divided into two groups:
  - Descriptive
  - Analytical
- Whereas descriptive studies are usually not used for hypothesis testing, they can often provide data for hypothesis generation
- In analytical studies, conversely, we use individual data for hypothesis testing by correlating exposure levels to the risk of outcome

Summary (2)

- As much as we would like to be able to, experimental studies are often unethical, impractical or impossible to conduct
- Therefore, observational studies are often the only alternative

Summary (3)

- There is a more or less generally accepted evidence hierarchy of the different study designs:
  - RCTs (and variations thereof)
  - Cohort studies
  - Case-control studies
  - Cross sectional studies
  - Ecological studies
  - Case series
  - Case reports