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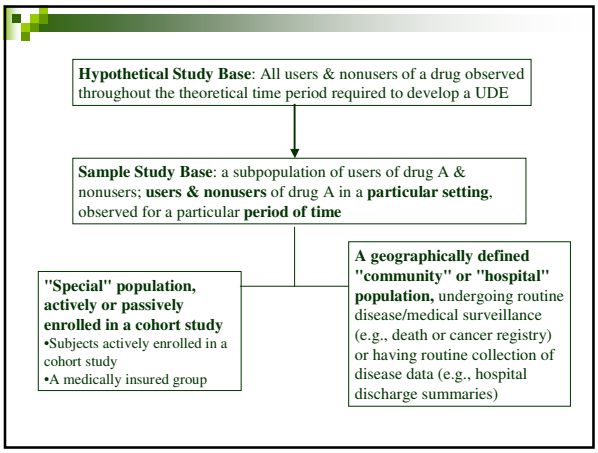
Observational Study Design

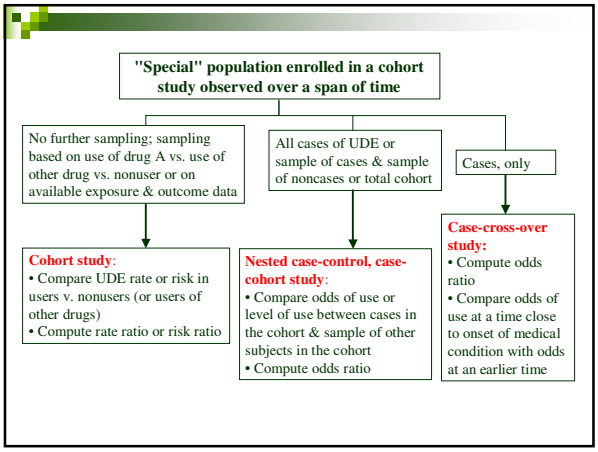
- **Analytical** observational studies
  - Quantify adverse or beneficial effects by measuring associations with rate, risk, odds ratios or with rate or risk differences
  - Types
    - Cohort studies
    - Standard/conventional population- or hospital-based case-control studies
    - Hybrid studies
      - Nested case-control studies
      - Case-cohort studies
      - Case-crossover studies

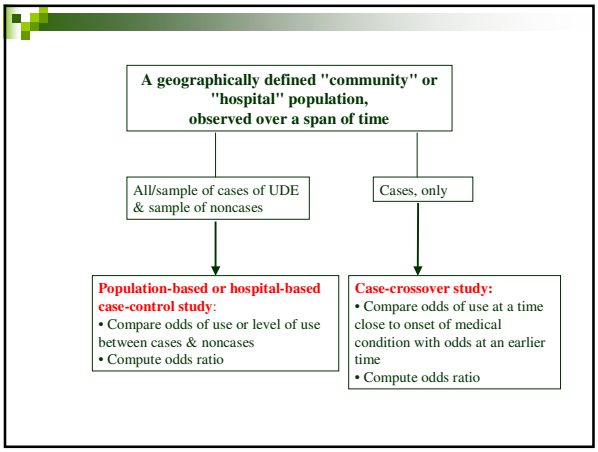
Hybrid Studies. Definition

- Composite designs that combine elements of two basic designs (e.g. cohort designs and case-control studies), or
- Combines elements of a basic design with elements of a non-observational design.

Kleinbaum D, Epidemiologic Research, 1982:70-71

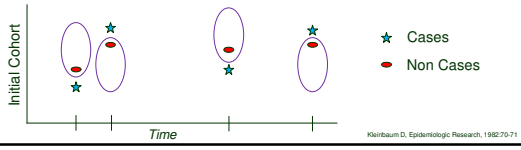

Hypothetical Study Base: All users & nonusers of a drug observed throughout the theoretical time period required to develop a UDE
Sample Study Base: a subpopulation of users of drug A & nonusers; **users & nonusers** of drug A in a **particular setting**, observed for a particular **period of time**
"Special" population, actively or passively enrolled in a cohort study
•Subjects actively enrolled in a cohort study
•A medically insured group
A geographically defined "community" or "hospital" population, undergoing routine disease/medical surveillance (e.g., death or cancer registry) or having routine collection of disease data (e.g., hospital discharge summaries)


"Special" population enrolled in a cohort study observed over a span of time
No further sampling; sampling based on use of drug A vs. use of other drug vs. nonuser or on available exposure & outcome data
All cases of UDE or sample of cases & sample of noncases or total cohort
Cases, only
Cohort study:
• Compare UDE rate or risk in users v. nonusers (or users of other drugs)
• Compute rate ratio or risk ratio
Nested case-control, case-cohort study:
• Compare odds of use or level of use between cases in the cohort & sample of other subjects in the cohort
• Compute odds ratio
Case-cross-over study:
• Compute odds ratio
• Compare odds of use at a time close to onset of medical condition with odds at an earlier time

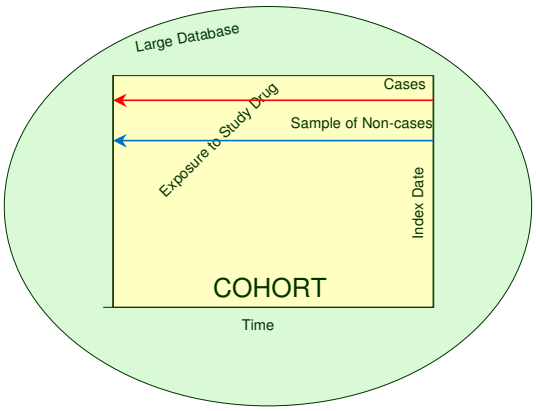

A geographically defined "community" or "hospital" population, observed over a span of time
All/sample of cases of UDE & sample of noncases
Cases, only
Population-based or hospital-based case-control study:
• Compare odds of use or level of use between cases & noncases
• Compute odds ratio
Case-crossover study:
• Compare odds of use at a time close to onset of medical condition with odds at an earlier time
• Compute odds ratio

Nested Case-Control Studies

- Combines elements of cohort and case-control designs.
- A defined population (cohort) is followed for a period of time until a number of incident cases of a disease/outcome are identified. At specific point in time, all cases and a sample of non-cases are compared with regard to prior exposure to a risk factor.



Kleinbaum D, Epidemiologic Research, 1982:70-71



Nested Case-Control Study

PAST		PRESENT
POPULATION CAN BE WELL DEFINED	→	IDENTIFY CASES IN WELL-DEFINED POPULATION
	←	SELECT SAMPLE NONCASES FROM SAME POPULATION
EXPOSURE	←	INTERVIEW/REVIEW RECORDS CASES/NONCASES ABOUT PAST EXPOSURES

Hartzema A, Porta M, Tilson H. Pharmacoepidemiology, 1998:92

Example

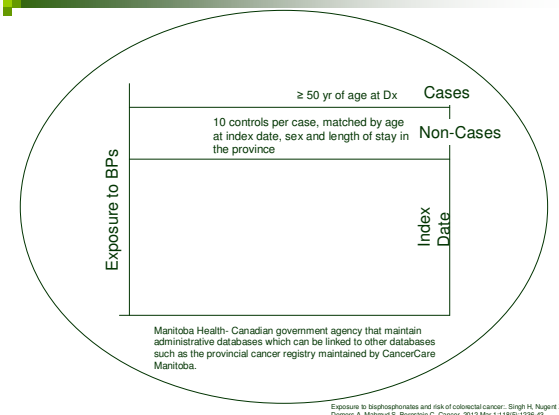
Exposure to bisphosphonates and risk of colorectal cancer:. Singh H, Nugent Z, Demers A, Mahmud S, Bernstein C. Cancer. 2012 Mar 1;118(5):1236-43

BACKGROUND: Chemoprevention is a potentially attractive strategy for decreasing the burden of colorectal cancer (CRC). Preclinical studies suggest that bisphosphonates (BPs) may have direct antitumour effects against CRC through the inhibition of angiogenesis, invasion and adhesion of tumor cells, and overall tumor progression and can stimulate adoptive and innate immunity. The objective of this study was to determine the effect of exposure to BPs on the incidence of CRC.

METHODS: The Manitoba Cancer Registry was used to identify patients who were diagnosed with CRC from 2000 to 2009 who had been living in Manitoba for at least 5 years before diagnosis (cases). Each case was matched to 10 controls of similar age, sex, and duration of residence in Manitoba using incidence density sampling. Exposure to BPs was determined using the provincial Drug Program Information Network database. Conditional logistic regression analysis was performed to determine the effect of exposure to BPs on CRC incidence with adjustment for health care use, medical procedures (including lower gastrointestinal endoscopy), socioeconomic status, and pre-existing health conditions.

RESULTS: In total, 5425 patients with CRC were matched to 54,242 controls. In the multivariate analysis, exposure to BPs was associated with a reduction in the risk of CRC (2-13 BP prescriptions over ≥5 years: odds ratio [OR] 0.84; 95% confidence interval [CI], 0.71-1.00; ≥14 BP prescriptions over ≥5 years: OR, 0.78; 95% CI, 0.65-0.94). When the effect of specific BP agents was evaluated, the effect was significant only for exposure to risedronic acid (OR, 0.50; 95% CI, 0.30-0.85). There was no significant effect of increasing duration or cumulative dose of alendronic acid.

CONCLUSIONS: The results from this study suggested that exposure to BPs, especially risedronic acid, may be associated with a decreased risk of developing CRC.



Manitoba Health- Canadian government agency that maintain administrative databases which can be linked to other databases such as the provincial cancer registry maintained by CancerCare Manitoba.

Exposure to bisphosphonates and risk of colorectal cancer:. Singh H, Nugent Z, Demers A, Mahmud S, Bernstein C. Cancer. 2012 Mar 1;118(5):1236-43

Odds Ratios and 95% Confidence Intervals for the Association Between Colorectal Cancer and Exposure to Bisphosphonates: Conditional Logistic Regression Analysis

No. of Bisphosphonates Prescriptions	OR	95% CI
[illegible]		
0-1	1.00	--
[illegible]	[illegible]	[illegible]
≥ 14	0.78	0.65-0.94

* Adjusted by history of previous exposure to lower gastrointestinal endoscopy, SES, exposure to hormone-replacement therapy and NSAIDs, physician visits, Charlson comorbidity index

Exposure to bisphosphonates and risk of colorectal cancer:. Singh H, Nugent Z, Demers A, Mahmud S, Bernstein C. Cancer. 2012 Mar 1;118(5):1236-43

Case-Cohort Studies

- Similar to nested case-control study, but the non-cases (controls) are selected randomly from the original cohort.
- Economic alternative to a standard cohort study.
- It allows direct estimation of risk ratios without the assumption that the disease under study is rare.

Prentice RL. 1986;73:1-11

Case-Cohort Studies

- Exposure or covariate information is collected only for a random subcohort, as well as for all participants who have experienced the event of interest.
- It is an efficient model because there is not collecting exposure and covariate information on noncases outside the subcohort

Case-Cohort Design. Example

Angiotensin-converting enzyme and angiotensin II receptor subtype 2 genotypes in type 1 diabetes and severe hypoglycaemia requiring emergency treatment: a case cohort study. Pharmacogenet Genomics. 2009 Nov;19(11):864-8.

Abstract
AIMS:
In type 1 diabetes, individual susceptibility to severe hypoglycaemia is likely to be influenced by genetic factors. We have previously reported an association of the deletion (D-) allele of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism and the A-allele of the angiotensin II receptor subtype 2 (AT2R) 1675 G>A polymorphism with risk of severe hypoglycaemia in such patients. The aim of this study was to test the hypothesis that these alleles are more frequent in patients suffering from the most severe episodes of hypoglycaemia requiring medical emergency treatment.
METHODS:
The case cohort study consisted of 108 cases of type 1 diabetic patients with severe hypoglycaemia requiring medical emergency treatment during a 1-year period and 262 consecutive controls without such events. ACE I/D and AT2R 1675G>A genotype distributions were compared between cases and controls.
RESULTS:
The proportion of D-allele carriers was higher amongst cases than controls (83 vs. 73%; P=0.032). In contrast, AT2R genotype distribution was similar in cases and controls. In a multiple regression analysis, D-allele carriage remained a significant risk factor for being a case [odds ratio: 1.9 (1.0-3.6)] together with male sex, impaired symptomatic awareness of hypoglycaemia and presence of nephropathy.
CONCLUSION:
The D-allele of the ACE gene is associated with severe hypoglycaemia requiring emergency treatment in type 1 diabetic patients with preserved spontaneous ACE activity. This supports the association between high ACE activity and occurrence of severe hypoglycaemia.

Case-Crossover Design

- Introduced in 1991 by Maclure.
- Efficient alternative to the case-control approach.
- It assess the relationship between **transient exposure and acute outcomes** in situations where the control series of a case control study is difficult to achieve.
- **Subjects serve as their own matched controls** with defined by prior time periods in the same subject.
- All control person-moments prior to the outcome event are selected

Maclure M. Am J Epidemiol 1991;133(2):144-153; Hebert C, et al. Pharmacoepidemiol Drug Saf 2007;16 (8):845-9. Delaney JC. Stat Methods in Medical Research 2009;18:53-65.

Case-Crossover Design

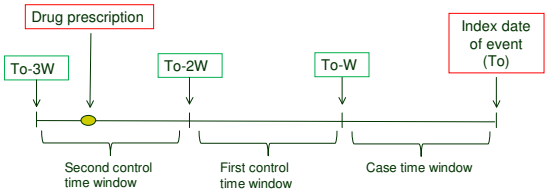
Case-Crossover Design

- Each case contributes one case window and one or more control windows.
- The case window is defined as the “at risk” period preceding the event.
- Control windows are periods of the same length as, and not overlapping with, the case window that provide an estimate of the expected frequency of exposure of each case.
- It requires careful documentation of the exact timing of the onset of the case disease

Stang A, Jockel KH. European J of Epidemiol, 2004;19:527-532

Case-Crossover Design

- It uses the difference in exposure rates just before an event (case) with those at other time points in the subject's history (controls) to estimate an odds ratio of the outcome associated with exposure.



Maclure M. Am J Epidemiol 1991;133(2):144-153; Hebert C, et al. Pharmacoepidemiol Drug Saf 2007;16 (8):845-9. Delaney JC. Stat Methods in Medical Research 2009;18:53-65.

Case-Cross-over Designs

- It assumes that the duration of the change in risk is constant
- The estimates are sensitive to misspecification of the exposure time window
- Results will be affected if subjects modified their behavior on the basis of prior experience with similar outcomes or related symptoms
- Information bias is possible. Information may not be available for individuals who refused to participate or were eliminated
- Selection bias based on disease severity is often an issue

Case-Crossover Design. Example

Effect of anticoagulant warfarin on the risk of GI bleeding using the GPRD. Delaney C, Suissa S

- All first-ever cases of GI bleeding in the GPRD 2000-2005
- At least 3 years of clinical data recorded in the database at the time of first GI bleed.
- Warfarin exposure (prescriptions) during the window period
- Control periods: two time periods immediately preceding the 90-day risk period
- There were 4028 cases of GI bleeding (4.3% received warfarin in 30 days prior to diagnosis)

Statistical Methods in Medical Research 2009;18:53-65

Case-Crossover Design. Example

Effect of anticoagulant warfarin on the risk of GI bleeding using the GPRD. Delaney C, Suissa S

Exposure Classification	Rate ratio	95% CI
Stratified case crossover		
Reference	1.00	Reference
Warfarin	0.98	0.74-1.28
Warfarin (1-3 Rx in past year)	2.59	1.42-4.74
Warfarin (4-6 Rx in past year)	0.75	0.56-1.02
Case crossover with 1-year lag in exposure window		
Reference	1.00	Reference
Warfarin	1.29	1.00-1.67

Statistical Methods in Medical Research 2009;18:53-65

Q&A