Population based studies in Pancreatic Diseases

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Definition

- Population-based studies aim to answer research questions for defined populations\(^1\)
- Generalizable to the whole population addressed in the study hypothesis, not only to the individuals included in the study\(^1\)

Types
- Case-control
- Cross-sectional
- Twin studies
- Prospective and Retrospective cohort studies

- Individuals that are included into the study –should be representative of all individuals in the a priori defined specific population

\(^1\)Roselind Lieb, Reference Work Entry, Encyclopedia of Behavioral Medicine pp 1507-1508
Context

• Are they relevant?
  • In the context of Randomized Control Trials (RCTs) and Basic Science Research

Yes!!!
## Population based studies vs RCT

### Population based studies
- Good external validity
- Provide insight into delivery of care in routine practice to all patients, including elderly and those with comorbidity
- Provide information to guide future knowledge translation
- Can provide evidence of effectiveness of new therapies in the general population
- Large samples provide the opportunity to study rare diseases for which RCTs are not possible
- Can provide insight into short- and long-term toxicity in routine practice
- **Can address questions that have not, and will not, be evaluated in an RCT**

### RCT
- Excellent internal validity
- Provide precise measures of efficacy and acute toxicity of new therapies under ideal conditions
- Because of randomization, measurement of effect size is less prone to bias
- Allow exploratory measures of secondary endpoints, including patient-reported outcomes and aspects of correlative biology
- Can evaluate prognostic and predictive properties of new biomarkers and cancer therapies
- Provide a mechanism whereby new (and potentially toxic) treatments can be carefully studied in centers of excellence

Characteristics

• Longitudinal assessment of exposure-outcome relations
• Can evaluate multiple hypotheses
• External validity
• Estimate distributions and prevalence rates
• Assess risk factor trends over time
Important Issues in population based studies

• Novel research questions
  • Valid definition
• Identification of population (ideal database)
• Methodological expertise
• Subject matter expertise/ Mentor/ Senior faculty
• Collaborations
• Impact on patient management

1Roselind Lieb, Reference Work Entry, Encyclopedia of Behavioral Medicine pp 1507-1508
Data Resources

• Agency for Healthcare Research and Quality (AHRQ)- Healthcare Cost and Utilization Project (HCUP)
  • National Inpatient Sample (NIS)
  • Nationwide Emergency Department Sample (NEDS)
  • Kids Inpatient Database (KIDS)
  • State Inpatient Database (SID)
  • Nationwide Readmission Database (NRD)
• Veterans administration (VA) database
• Surveillance Epidemiology and End Results (SEER)
• National Cancer Database
• Market Scan
• North American Pancreatitis Study (NAPS)
• Maryland HSCRC database
• Kaiser Permanente
• Biomedical Informatics
• Many other..
Questions that can be addressed only by population based studies

- Acute Pancreatitis (AP)
- Chronic Pancreatitis (CP)
- Pancreatic cysts
- Pancreatic Cancer (PDAC)
Population based studies - AP

• AP is the one of the most common GI causes of hospital admission in the US\(^1\)
  • 274,119 discharges in 2009 and cost $2.6 billion
• Annual incidence 13-45/ 100,000 persons\(^2\)-\(^4\)
• AP Etiologies: biliary (28%), alcohol (19%) and idiopathic (36%)\(^5\)
  • Readmissions following a sentinel attack of AP are common (29%)
  • Progression to CP is infrequent and usually occurs in the setting of RAP, alcohol, and smoking
• Readmission after AP is influenced by demographics, etiology, and subsequent CP diagnosis\(^6\)

\(^1\)Peery A, et al. GASTROENTEROLOGY 2012;143:1179–1187

Background: ↑ AP incidence, ↓ case-fatality rate

Aims: Case-fatality may not capture delayed mortality, therefore evaluating AP deaths in population would be unbiased
Findings:

• Confirmed the trends in increasing hospitalizations and decreasing case-fatality for AP
• Decreased population mortality for AP
• True increase in burden of AP, severity and no change in population mortality is related to medical advances in the management of AP
Heavy Smoking Is Associated With Lower Age at First Episode of Acute Pancreatitis and a Higher Risk of Recurrence

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• **Data Source:** Veteran Health Administration (VA) data from 1998-2007 (n=484,624; AP=6799 pts)
• **Background:** Smoking association with RAP and CP established; limited knowledge on smoking and AP
• **Aims:** Cigarette smoking on AP risk and clinical presentation in pts with and without alcohol
Findings:

• Smoking is an independent risk factor for AP
• Smoking augmented the risk of AP in heavy alcoholics
• Smoking and alcohol were independently associated with lower mean age at the time of first attack of AP and higher risk of recurrence (≥ 4 episodes)
• **Data Source:** Nationwide Readmission Database (NRD) 2013 (n=178,541 AP pts)

• **Background:** 30-day readmission rate for AP regarded as a quality metric predictor for 1 yr mortality. Data from single centers; readmissions to other hospitals not accounted for;

• **Aims:** Frequency of readmissions, independent predictors, causes of readmission and aggregate costs $
Findings:

• 14% of index admissions had 30-day readmissions (5% related to pancreatitis)
• Confirmed alcohol and idiopathic etiologies had ↑ risk of readmissions
• Acute biliary AP pts with index cholecystectomy had ↓ risk of readmissions and better outcomes
• Cholecystectomy should be performed in acute biliary AP pts as per recommended guidelines
Population based studies - CP

• Annual incidence 5-12/100,000 persons and prevalence 50/100,000 persons\textsuperscript{1-2}

• Danish National Registry had shown that the risk of fractures was higher in younger patients with CP\textsuperscript{3}

• High Prevalence of Low-Trauma Fracture in Chronic Pancreatitits- from Partners Research Patient Data Registry (RPDR)\textsuperscript{4}

\textsuperscript{1}Hirota M, et al. Pancreatology. 2012;12:79–84
Chronic Pancreatitis and Fracture

A Retrospective, Population-Based Veterans Administration Study

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• **Data Source:** Veteran Health Administration (VA) data from 1999-2006 (n=453,912; 3257 CP pts)

• **Background:** CP and metabolic bone disease, especially in females; limited knowledge in males

• **Aims:** Association of CP and metabolic bone disease across sex (males) and age
Findings:
• Confirmed CP pts had ↑ risk of osteoporotic fractures
• CP pts had higher risk (3x) of hip fractures compared to pts without CP
• Male CP pts aged 45-65 and 65+ had an ↑ risk of osteoporotic fractures compared to controls

Conclusions: All CP pts ≥ 45 yrs irrespective of sex be screened for bone mineral density. Simple in-office cost-minimizing screening strategies for metabolic bone disease in CP needs to be developed
Population based studies - Cysts

• Incidence of malignancy in pancreatic cysts was 0.4% per year during surveillance (n=1,735) using Southern California database\(^1\)
  • Included PDACs diagnosed after at least 3 months of cyst
  • Average duration of surveillance was 23.4 months
• Prevalence of mucin-producing adenocarcinoma in pts with pancreatic cysts by using a population-based cross-sectional methodology\(^2\)
  • 33.2 of 100,000 U.S. patients aged 40 to 84 years have malignant transformation of pancreatic cysts

Data Source: Veteran Health Administration (VA) data from 1999-2006 (n=520,970; pancreatic cysts=755)

Background: ↑ detection of asymptomatic pancreatic cysts; Mucinous cysts and IPMNs have malignant potential; risk of malignancy in benign cysts incidentally noted on abdominal imaging has not been established.

Aims: Overall long-term risk of pancreatic cancer in patients with pancreatic cystic lesions (observation period -8 years)
Findings:

• Pancreatic cancer was diagnosed in 2.3% (17/755) of pancreatic cysts
• Overall risk (hazard ratio) was 19.6 times greater than patients without pancreatic cysts
• Cysts without a history of AP/CP, risk of pancreatic cancer was 18.8 times greater than patients without pancreatic cysts
Population based studies - PDAC

- Global annual incidence rate for pancreas cancer is about 8/100,000 persons\(^1\)
  - US- 12.5/ 100,000 persons
  - Incident cases (yearly)- 53,670
  - Prevalence ~60,000-75,000

https://www.seer.cancer.gov
• **Data Source:** Nationwide Inpatient Sample (NIS) 1998-2011 (n=151,454)

• **Background:** Significant improvements in understanding of natural history and treatment options for pancreatic diseases; no population-based studies to evaluate the impact on surgery trends;

• **Aims:** To determine the change in indications, frequency and type of operations performed
Findings:
• Operations performed during 1998-2011 almost doubled
  • 80% pancreatic resections
  • 65% for malignant or benign lesions
• Significant change in type and indications of procedures was noted
• Improved outcomes of short length of stay and ↓ in-hospital mortality

Conclusion: ↑ % of operations for older, comorbid pts reflect changing population distribution, advances in medical knowledge, improvement in surgical techniques, technology and availability of new treatment options
Data Source: Veteran Health Administration (VA) data from 2000-2007 (n=495,504; AP=5720 pts; PDAC= 710 pts)

Background: AP is often the initial presentation of PDAC; prior literature on AP-PDAC cross-sectional; temporal relationship could not be evaluated

Aims: % of patients with PDAC who had AP before a cancer diagnosis, % of patients with AP who were subsequently diagnosed to have PDAC and identified patient characteristics that were associated with a high risk of PDAC diagnosis after an AP attack
Findings:

- 12.1% of PDAC had AP before cancer diagnosis
- 10.7% had AP < 2 yrs of PDAC
  - >50% of these had PDAC diagnosis delayed by more than 2 months after AP episode
  - 1.5% of AP pts had a PDAC diagnosis
- Risk ↓ after 1\textsuperscript{st} year of AP episode
- Negligible in pts < 40 yrs and ↑ steadily with age (>40 yrs)

Conclusion: Patients with AP after 40 years of age have ↑ risk of PDAC diagnosis within the following 24 months
New Diagnosis of Chronic Pancreatitis: Risk of Missing an Underlying Pancreatic Cancer

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- **Data Source:** Veteran Health Administration (VA) data from 1998-2007 (n=471,992; PDAC=917; pre-existing CP=2,557; New diagnosis CP=2,175)

- **Background:** Pts with PDAC sometimes present with symptoms suggestive of CP; % of PDACs that may be misdiagnosed as CP, the resultant delay in cancer diagnosis, and the number of pts with new diagnosis of CP who may actually have an underlying PDAC is unknown

- **Aims:** % of pts with PDAC who are initially misdiagnosed as having CP, % of pts with new diagnosis of CP who are subsequently diagnosed to have PDAC, and pt characteristics associated with a higher likelihood of subsequent PDAC diagnosis
Findings:

- 5% of pts with PDAC are initially misdiagnosed as CP
  - 2/3rd of these pts had cancer diagnosis delayed by > 2months
- 2% of new diagnosis CP had underlying PDAC
- Risk Negligible in pts < 40 yrs and ↑ steadily with age

Conclusion: Reliable exclusion of PDAC before a CP diagnosis in patients aged >40 years, and especially those without heavy alcohol or smoking history, can avoid delay in cancer diagnosis and potentially help diagnose more early-stage PDACs
Generalizing beyond study population

- Limit applicability if circumstances of exposure of interest (e.g., duration, time of exposure) vary over time
- Differences in susceptibility to risk factor of interest between study population and populations to which one wishes to apply study findings
- Populations with different levels of exposure
- Confounding variables differ between study population and populations
- Definitions of exposure and outcome may not be applicable
- Association between risk factor and clinical outcome influenced by prevalence of underlying subclinical process
- Risk factor and outcome associations are time dependent (length of follow-up needs to be accounted for in generalizing)
Strengths

• External Validity
• Can address questions that have not, and will not, be evaluated in an RCT
• Highlight the regional/ national differences in prevalence
• Clinical relevance, impact on clinical practice
• Possibility of population-based screening
Limitations

• Limited internal validity
• Some databases are collected for administrative billing purposes (and not primarily for clinical research)
• ICD 9 / ICD 10 codes – accuracy?
• Not granular (detail oriented) compared to patient charts
  • Comorbidity, performance status, and specific treatment plan
• Bias
  • Confounding by indication for a given treatment
  • Concurrent changes in practice and/or disease biology
• Large databases- sometimes overwhelming
Knowledge gaps

• Long term risk of pancreatic cancer
  • Particularly in the context of pancreatitis
  • Pancreatic cysts

• New-onset Diabetes and Pancreatic cancer

• Diabetes, Chronic Pancreatitis and Pancreatic cancer
Thank you!