Trends in 21st Century Epidemiology: From Scientific Discoveries to Population Health Impact

Session 4: Use of epidemiologic research to advance clinical and public health practice: bridging the evidence gap with observational studies and randomized clinical trials

Moderator: Sheri D. Schully, Ph.D., Division of Cancer Control and Population Sciences, NCI

Epidemiology and evidence-based research along the cancer care continuum

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Panel and Audience Discussion

- What are new ways in which epidemiology can be used to fill evidence gaps between discoveries and population health impact in the cancer care continuum?
- How can observational epidemiology make the greatest scientific contributions in understanding cancer-related risk factors that cannot be studied through randomized clinical trials?

..

Cultivate Observational Cohorts

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1. Definition, Importance
2. Past
   -examples, lessons
3. Future
   -opportunities, challenges, recommendations

Cultivate Observational Cohorts

Definition (of cohort): defined group followed over time

Importance:

Can cohort be used to answer question(s)?

- Cohort can have “strong design” for questions of diagnosis, prognosis, response to rx (molecular markers) [RCT better, but may be not appropriate or impossible.]
- *Strength of design* to answer question *is* related to features:
  -fair ‘comparison’ (avoid bias) for quest.: internal validity
  -relevant question: external validity
  -details: ascertain baseline state, exposure, outcome, etc.

Devils in design/detail. One ‘wrong’ feature can be fatal.

Cultivate Observational Cohorts

"Observational" does *not* mean:

- "passive" (e.g., PI is passive; or 'no design')
- "annotated specimens" + "technology/data" + "bioinformatics"

*Concept: "Specimens and data=product of a **study**.*

With cohort data, you have to fashion a "study"
(regarding comparison, bias, relevance, etc.)
and describe it in Methods.

It's not "data+analysis."

It's a "study," whether thought about/not.

Ransohoff. *JCO* 2010;28:698

Cultivate Observational Cohorts

In cohorts that already exist, can strong design be arranged?

1. PI imagines ideal ***design***: specify question, data source, comparison, anticipate/avoid bias, etc.
2. PI asks “In existing cohort, is *inherent design* close to ideal?” Could *added design* make it, overall, satisfactory, to answer that question?”

Concepts

- ***Design*** *(inherent, added) determines study strength.*
- *If don’t think about design early (re kinds of data, comparison, relevance), may limit kinds and strength of questions that can be addressed later.*

Examples of Observational Cohort: Mostly T1, Lessons for Other Ts

(From Khoury et al., *Am J Epidemiol*. 2010 September 1; 172(5): 517–524 with permission of Oxford University Press.)

Table 1. Epidemiology and the Phases of Translation and Knowledge Synthesis—From Discovery to Population Health Impact

Phase	Details	Role of Epidemiology	Examples From Genomics
T0	Description and discovery	Describing patterns of health outcomes by place, time, and person; finding determinants of health outcomes by use of observational studies	Describing patterns of health outcomes in relation to inbreeding, migration, and family history to generate hypotheses about genetic factors; genome-wide association studies as a tool for gene discovery
T1	From discovery to health applications (tests, interventions)	Characterizing discovery and assessing potential health applications by using clinical and population studies	Assessing prevalence, associations, interactions, sensitivity, specificity, and predictive value of testing for genetic risk factors
T2	From health application to evidence guidelines	Assessing the efficacy of interventions to improve health and prevent disease by using observational and experimental studies	Assessing the clinical utility of genetic risk factors in improving health outcomes
T3	From guidelines to health practice	Assessing the implementation and dissemination of guidelines into practice	Assessing the factors associated with implementation of *BRCA* testing in practice
T4	From health practice to population health outcomes	Assessing the effectiveness of interventions on health outcomes	Assessing the effectiveness of newborn screening programs
Knowledge synthesis	Systematic review of what we know and what we do not know and how we know it	Knowledge synthesis applies to all phases of translation by use of evidence synthesis and systematic reviews.	T1—evaluating the credibility of genetic associations and assessing the genetic effects and interactions (through HuGENet) T2—systematic reviews on the clinical validity and utility of genomic applications for specific intended uses (through EGAPP appraisal)

Abbreviations: EGAPP, Evaluation of Genomic Applications in Practice and Prevention; HuGENet, Human Genome Epidemiology Network; T0–T4, designated phases of translational research.

Examples of Observational Cohort: Mostly T1, Lessons for Other Ts

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includes etiology

diagnosis, prognosis, etc

RCTs/outcome

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T2	From health application to evidence guidelines	Assessing the efficacy of interventions to improve health and prevent disease by using observational and experimental studies	Assessing the clinical utility of genetic risk factors in improving health outcomes
T3	Fr...	Assessing the implementation and dissemination of guidelines into practice	Assessing the factors associated with implementation of *BRCA* testing in practice
T4	From health practice to population health outcomes	Assessing the effectiveness of interventions on health outcomes	Assessing the effectiveness of newborn screening programs
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In examples, consider design, lessons

Design

- -What is *inherent;* what is *added*?
- -How much effort to *add*?
- -Did *overall* design have strength to answer question?

Lessons

- -How, in future, to cultivate observational cohorts that are strong?

1. Prognosis BrCa

Paik S et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *NEJM*. 2004; 351: 2817.

Question

- In node-neg BrCa, is prognosis (i.e., low recurrence rate) discriminated by RNA signature?

Inherent design

- In banked RCT, control group followed: dx to outcome.

Added design

- measure RNA in FFPE specimen at diagnosis

Results

- RNA signature prognostic: low recurrence rate

1. Prognosis BrCa

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Lessons

- Inherent design has RCT strength: ascertain l.t. outcome, blinded, etc; clear relevant question
- Piggybacking (adding) to strong inherent design: useful, if possible
- This example:

  - NIH-funded, already banked

  - **“Old” study can assess new molecules (validation or discovery)**

  Future: add ‘specimens’ to selected studies?

2. Diagnosis OvCa (blood)

Zhu CS et al. A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. *Can Prev Res*. 2011; 4: 375.

Question

- Can blood proteomics screen for OvCa?

Background

- Strong claims (2002), disappointment (2002-8) b/o weak design (bias in comparison etc.)

Inherent design

- RCT (PLCO) ~1990; biorepository added mid-1990s, included serial bloods.

Added design ~2008

- elect a blood just <dx for proteomics assay
- blinded hypothesis testing'

Result

- 5 groups' assay panels: no better than CA125.

2. Diagnosis OvCa (blood)

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Lessons

- Diagnosis question addressed by serial specimens (blood), by selecting blood near time of diagnosis.
- Expensive, difficult (big N subjects, specimens; small N cancer and of “relevant specimens”)
- NIH-funded; NIH arranges strong comparisons
- “Old” study can assess new molecules
- “If only bigger”... (what lessons from ‘mega-cohort’)

3. Diagnosis CRC (stool DNA)

Imperiale TF et al. Fecal DNA versus occult blood for colorectal-cancer screening in an average-risk population. *NEJM*. 2004; 351: 2704.

Question

- Can stool DNA screen for early CRC?

Inherent design

- prospective cohort; industry (EXACT) DNA assay
- expensive: specimen<colonoscopy;
  >5000 persons, 31Ca

Added design: (none)

Result

- bad news: better than gFOBT, but expensive;
  biologically promising, clinically disappointing
- good news: answer strong (reliable) because of design

3. Diagnosis CRC (stool DNA)

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Lessons

- If was greater amount of stool or blood, others could study new molecules (validation or discovery).
- Industry resource is not ‘shared.’

4. Outcome CRC screening

Selby JV et al. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *NEJM*. 1992; 326 (10): 653.

Question

Can sigmoidoscopy reduce CRC mortality in L colon?

Inherent design (1970s+)

HMO cohort, some sig screening was done

Added design (years later)

- nested case-control study
- learn cause of death
- learn whether exposure occurred (sig for screening)
- create internal control group

4. Outcome CRC screening

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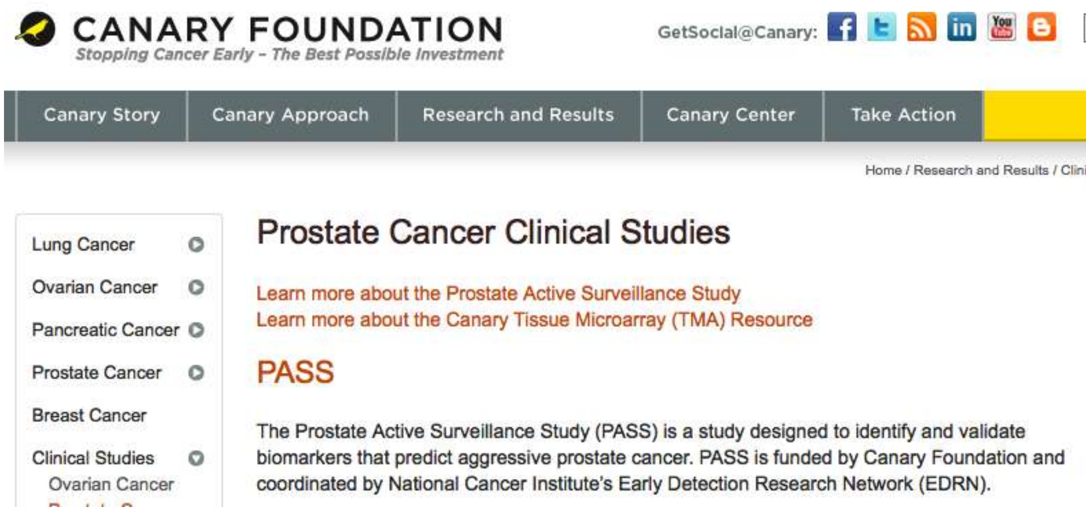
Result

L-sided CRC mortality reduced ~60%.

Lesson

- Assess RCT question in case-control (observ.) study.
- Strength: nested c-c; exposure reason known.
- Could one add bloods, other specimens, and answer other questions.

5. PrCa Prognosis



Question

- Can markers identify lethal vs non-lethal PrCa?

Inherent design (PASS)

- Prospective cohort, N>1000, active surveillance.

Added design: (none)

Results: (none)

Comment

- If ‘lethal’ PrCa is rare, are results limited?

Lesson

- Cohorts may have limitations.

Obervational cohorts cultivate: other examples

a) *Research studies* designed as RCT, cohort

- -Framingham
- -Nurses Health Study; Physicians Health
- -WHS

(used to study diagnosis, prognosis, etc)

b) *Practice settings*

- -HMOs (Kaiser-Permanente, Group Health, etc)
- -Eli Lilly etc
- -other

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Examples and concepts are not new to this group.

Our focus: Lessons about how to cultivate observational cohorts.

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Future: Opportunity

An illustrative example:
Molecular markers (blood) for CRC screening

Background

- In design to discover/validate molecular test, specimen (e.g. blood) must be obtained <procedure; req. big N.
- What cohorts could be cultivated?
    - In existing cohort infrastructures, add spec. collection (RCTs of EU, VA; HMOs; practices)
- Specimens could be used for validation and/or discovery.

Future: Opportunity

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- Specimens could be used for validation and/or discovery.

-Imagine big N, big volume of blood, stool;

then banked specimens useful in discovery/validation.

Approach is generalizable to many problems.
Challenges: logistics, motivation.

Future: Challenges

What available cohort sources, infrastructures

- -ongoing research studies
- -practice settings
- -e.g., CRN, HMORN, HMOs; Cohort Consortium; etc etc

What are logistics of ‘cultivating’

- -How to anticipate questions and technologies; impact on “design”
- -*Add* what?
- -Who ‘drives’ research if different from who ‘owns’ data?
  - •*non-trivial: consider CRN, co-op groups*

Future: Challenges

Other challenges:

- how to cultivate efficiently; avoid wasted effort (past examples)

Recommendation: **Cultivate observational cohorts**

But how?

1. Make sure we understand lessons of past; ideas not new.
2. Approaches
   - •big effort; big N of smaller studies (let 1000 flowers bloom)
   - •*piggyback* onto current infrastructure
   - •role of nested case-control design
   - • considering ‘megacohort’? *beware limitations*
3. Don’t just collect data/specimens/annotate; do consider role of questions, methods/*design* to answer, etc. .
4. Try different approaches, get preliminary data, scale up.

How to organize, supervise this effort...

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