Maximizing the Potential of Population-Based Cancer Registries to Inform Cancer Research

Presented by:

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Topics to be covered

• The importance of population-based cancer research (the concepts of Internal and External validity)
• Three ways population-based cancer registries can improve cancer research
• How population-based cancer registries relate to translational research
Two important concepts

- Internal validity
- External validity
### Animal Studies

<table>
<thead>
<tr>
<th>genetically identical mice</th>
<th>Developed Disease</th>
<th>Did not Develop Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed Animals</td>
<td>A</td>
<td>B</td>
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<tr>
<td>Unexposed Animals</td>
<td>C</td>
<td>D</td>
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</table>

Relative Risk = \( \frac{A}{A+B} / \frac{C}{C+D} \)
### Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Randomized trial (Prospective)</th>
<th>Study Outcome Occurred</th>
<th>Did not Occur</th>
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<tbody>
<tr>
<td><strong>Exposure or Intervention</strong></td>
<td>A</td>
<td>B</td>
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<tr>
<td><strong>No Exposure or Intervention</strong></td>
<td>C</td>
<td>D</td>
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</table>

Relative Risk = \( \frac{A}{A+B} \div \frac{C}{C+D} \)

**Random Allocation**
Internal Validity

• When differences between the experimental (exposed) group and the control group are completely accounted for, the study is said to have internal validity and causal inferences can be made.

• In other words, it is possible to determine whether the exposure causes some outcome (disease, etc.).

• Many have argued that “randomization” was the most important scientific advance of the 20th century.
(True or False) Findings from randomized clinical trials with strong internal validity usually have the same effect when they are applied to general populations?

1. True
2. False
External Validity

- When the findings from a research project or study can be generalized to some defined population, they are said to have **external validity**.
- Epidemiology (population science) provides the tools to explore **external validity** and many argue that moving from studies with strong **internal validity** to studies with strong **external validity** is the next step in advancing our scientific understanding.
- The continuum from research with strong internal validity to studies with strong external validity is also part of “Translational Research”.
Population-based cancer registries can improve cancer research in several important ways.
1. As a Population-Based Sample Frame

- Geographic Area Covered by the Population-Based Cancer Registry
- Cancer cases occurring each year
- Information gathered on each cancer case
- The Population-Based Cancer Registry

A scientific sample of data from cancer patients representing the population covered by the registry is provided to the researcher.

Cancer research with strong "external validity" (the ability to generalize the findings to the underlying population)
Intimate Partner Violence and Cancer Disparities

A novel population-based cohort study

- **Research Question:** Is IPV associated with delayed screening, late stage Dx or poor survival among women diagnosed with breast, colorectal or cervical cancer in Kentucky?

- **Design:** Population-based prospective cohort study

- **Methods:** KCR recruitment

- **Population-based Sample:** n=1,850

- **Results:** IPV (37% lifetime) Partner Interference (13%)
2. For Rapid Case Ascertainment

- Geographic Area Covered by the Population-Based Cancer Registry
- Pathology Labs (NLM Programs in Each Lab)
- Electronic Path (EPath) Reports for Cancer Patients Sent Automatically at the Time of Diagnosis

The Population-Based Cancer Registry Receives EPath Reports for more than 95% of All New Cancer Cases Diagnoses each Year

A population-based sample of cancer cases provided to the researcher

Cancer research with strong "external validity" (the ability to generalize the findings to the underlying population)

Biospecimens collected
High Arsenic, Chromium and Radon Levels and High Lung Cancer Rates in Appalachian Kentucky

(Top) Arsenic content and coal field locations in Kentucky; (Bottom) Incidence of lung cancer in the Appalachian versus Non-Appalachian region of Kentucky.
Geographic Area Covered by the Population-Based Cancer Registry

Pathology Labs

The Population-Based Cancer Registry

Formalin fixed paraffin imbedded tissue samples are collected from the labs by the Registry for a population-based sample of cases

A population-based sample of cancer case data and tissue are provided to the researcher

Cancer research with strong “external validity” (the ability to generalize the findings to the underlying population)
1. A retrospective cohort study using the registry as a virtual tissue repository to explore 5 distinct proteins associated with breast cancer recurrence

Purpose of the Study

Determine whether female breast cancer patients who were disease-free following surgery but subsequently had a recurrence of their breast cancer within five years had altered levels or activity of one or more of five proteins compared to women who were disease-free and did not have a recurrence.
The Five Proteins

• Par-4: pro-apoptotic tumor suppressor protein
downregulated during breast cancer recurrence

• Wnt/β-catenin: signaling pathway
  induces epithelial-mesenchymal transition (EMT)
  and promotes metastasis

• SNAIL, TWIST: transcription factors, promote EMT
  promote cancer progression (metastasis)
elevated in metastatic and recurrent tumors

• c-Abl, Arg: tyrosine kinases, oncoproteins
  promote survival, proliferation, and metastasis
  activity levels measured by pCrkL activity
A Retrospective Cohort Study

Using the Registry, all female breast cancer patients treated surgically between 2000 and 2007 at UK for their 1st Ca. and determined to be disease free were identified. Tissue blocks from the initial surgery were obtained for all of these patients, TMAs were constructed and stained to determine activity levels for each protein. This cohort was then traced forward in time to determine which patients recurred and which did not. (479 patients met the study criteria).

Comparisons were made between activity levels of each protein among the primary tumors of recurrent patients (59) and the non-recurrent patients (417).

For patients that recurred, comparisons were made between the tumor tissue at first surgery (the primary tumor) and the tissue taken at the time of recurrence. Tissue at the time of recurrence was only available for 22 patients.
### Preliminary Results

**PROTEIN EXPRESSION IN PRIMARY TUMORS FROM RECURRENT VS. NON-RECURRENT PATIENTS**

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<thead>
<tr>
<th></th>
<th>TWIST</th>
<th>SNAIL</th>
<th>PAR4</th>
<th>β-catenin</th>
<th>pCrkL</th>
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<tr>
<td><strong>Intensity</strong></td>
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<td>HER2+ (n=36)</td>
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<td>HER2-/ER+/PR+ (n=282)</td>
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<td>HER2-/ER-/PR+ (n=32)</td>
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<td><strong>Allred Score</strong></td>
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<td>HER2+</td>
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<td><strong>Intensity X Percent</strong></td>
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<td>HER2+</td>
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**H:** Significantly high in the primary tumor of recurrent patients

**L:** Significantly low in the primary tumor of recurrent patients
### PROTEIN EXPRESSION IN RECURRENT VS. PRIMARY TUMORS

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<td>Intensity x Percentage</td>
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**H**: Significantly high at the time of recurrence in the tissue sample of patient who recurred compared to their primary tumors
Preliminary Results

pCrkL EXPRESSION IN RECURRENT VS. PRIMARY TUMORS

Paired t-test P = 0.013
Wilcoxon Signed Rank P = 0.02
Conclusions

• Elevated levels of Twist, and low or not activated c-Abl/Arg (pCrkL) in HER2-/ER+/PR+ breast tumors may potentially serve as a novel biomarker for the recurrence of breast cancer.

• c-Abl/Arg was activated and over expressed in the tumors of patients at the time of recurrence. Inhibiting c-Abl/Arg activation may potentially prevent recurrence.

• It is difficult to imagine doing this study without using the Cancer Registry as a virtual tissue repository.
2. A Pre-Invasive Cervical Cancer HPV genotyping study

- Presented Wednesday morning at 10:30 AM in Concurrent Session E.
- Using the Registry as a virtual “population-based” tissue repository.
- Having the Registry serve as the honest broker for a study of this type.
(Multiple Choice) Within the next 5 years, do you think the central cancer registry in your state, province or city will participate in a study using the registry as a virtual tissue repository?

1. The central cancer registry in my state, province or city already participates in studies where the registry is used as a virtual tissue repository.
2. The registry is likely to participate in studies where the registry is used as a virtual tissue repository within the next 5 years.
3. The registry is unlikely to participate in studies where the registry is used as a virtual tissue repository within the next 5 years.
The final step in translational research is the broad based implementation of evidence based cancer research findings in the population.
From the **Laboratory** to the Population

Translational Research

- Genes
- Cells
- Animals
- Humans
- Populations

Basic Science
Clinical Science
Epidemiology
Quercitrin, a natural product from apple peel, is tested in an animal model to determine if it prevents UV exposure induced skin cancer.

Randomized trials in human populations

Broad application of the findings to the general population
From the **Population** to the Laboratory

And back again

Translational Research

Basic Science

Clinical Science

Epidemiology
Epidemiologic studies show that colorectal cancer is excessively high in the Appalachian area of Kentucky and this same population has high exposure to arsenic and chromium.

Cell line and animal studies are conducted to determine if exposure to arsenic and chromium contributes to the onset of colon cancer.
Carcinogenic metals in drinking water increased the multiplicity and size of colorectal tumors in the AOM/DSS-induced mouse colitis-associated colorectal cancer model.
Example

Cell line and animal studies are conducted to determine if exposure to arsenic and chromium contributes to the onset of colon cancer.

Epidemiologic studies show that colorectal cancer is excessively high in the Appalachian area of Kentucky and this same population has high exposure to arsenic and chromium.
From the **Laboratory** or the **Population**

Basic Science

Clinical Science

Epidemiology

Translational Research
The ultimate goal of translational cancer research is the wide-spread implementation of evidence-based research findings that significantly reduce the cancer burden in the population.

This includes the wide-spread implementation of evidence-based cancer control interventions.
More precisely defining the last phase of cancer related translational research

- Measuring the degree to which an evidence based intervention was implemented in the population.
- Identifying groups within the population for which the intervention was more or less effective.
- Measuring the degree to which the intervention had an impact on the cancer burden in the population.
- These are all aspects of “Implementation Science” and “Dissemination Research”.
- The population-based cancer registry is an essential tool for doing this type of research.
Thank You!

Questions?