Challenges in assessing disease latency for cancer in environmental epidemiology

Peggy Reynolds, Ph.D.
Case-only Clustering in Mobile Populations Workshop - November 11-12, 2010 - Ann Arbor, Michigan
Outline

• Latency
  • The concept
  • The problems
  • Windows of susceptibility

• Residential mobility
  • Studies of childhood cancers
  • Studies of breast cancer
Latency

• Typically defined as the period of time from initial exposure to a carcinogen and the date a cancer is diagnosed.
  • Sometimes defined by doubling time

• A few classic examples:
  • Asbestos exposure and mesothelioma (long latency)
  • Hiroshima/Nagasaki and leukemia (short latency)

• But this generally:
  • Assumes a one-hit theory of cancer causation
  • Fails to account for dose effects
  • Fails to account for timing effects
  • Fails to account for multifactorial influences
  • Fails to account for heterogeneity in cancers
  • Fails to account for genetic susceptibility
Windows of susceptibility

• Periods of life during which exposures may have the greatest effect

• Vary by cancer site and hypothesized mechanisms

• Have been most studied for the childhood cancers and breast cancer
Childhood Leukemia
Latency/windows of susceptibility

• Limited time frame for latency in children

• Some potentially key windows of susceptibility to environmental exposures:
  • Pre-conception exposures to mother/father
  • *In utero* exposures
  • First few years of life
  • Recent exposures
  • Lifetime cumulative exposures
Types of Childhood Cancer in California, 1988-94

- Leukemia: 35%
- Lymphoma: 9%
- CNS: 20%
- Germ cell: 5%
- Retinoblastoma: 3%
- Carcinomas: 3%
- Wilms: 5%
- Osteosarcoma: 2%
- All others: 18%
Childhood Leukemias (ages 0-14)
Percent Distribution by Type

Source: Cancer in California, 1988–1991
Age-Specific Incidence Rates of Child Leukemia - by Subtype

SEER 1976-1994
Causes of childhood leukemia

• The causes of 90% of childhood leukemias are unknown

• Known risk factors include:
  • genetic factors (eg. association with Down syndrome)
  • ionizing radiation (especially in utero exposures)
Viral Hypotheses for Childhood Leukemia

- Two-step mutations in progenitor B cells (Melvyn Greaves)
  - In utero (while immature B cells are rapidly dividing)
  - Later in childhood, especially among children without early exposures/immunity to common infectious agents

- New Towns (Leo Kinlen)
  - Direct exposure to specific viruses associated with population mixing
Childhood Leukemia and Indoor Pesticide Exposures

Ma et al., EHP, 2002
For GIS Studies What Address is Best?

• When is the biologically important time window of risk?

• Where do mothers/children spend the most time?

• Is residential mobility different by:
  - Demographic characteristics?
    • e.g. SES status?
  - Environmental exposures?
    • e.g. Proximity to traffic?
Percent of Block Groups in Each Quartile with Traffic Density Greater than 500,000 vmt/mi^2

Gunier et. al, J Exp Anal Env Epidemiol 2003
Population Under Five Years of Age Living in Block Groups with Traffic Density Greater than 500,000 vmt/mi²

Million Children

White  Hispanic  Asian/Other  Black

Gunier et al., J Exp Anal Env Epidemiol 2003
Percent of Income Quartile by Race Living in Block Groups with Traffic Density Greater than 500,000 vmt/mi²

Graph showing the percentage of income quartiles (Low, 2nd, 3rd, High) with different racial categories (White, Hispanic, Asian/Other, Black) plotted against traffic density.
San Diego Pilot Study Designed to Pretest Statewide Protocol

- Records-based study
- Use of GIS technology to assess exposures
- Control selection from birth files
- Effect of residential mobility
Case-Control Design

• *Cases (n=92):*
  1988-94 leukemia diagnoses under the age of 5 among children born to San Diego County mothers

• *Controls (n=368):*
  Children of the same gender, born the same day to San Diego mothers, and not known to have had cancer
Two Risk Factors of Interest

• Socioeconomic Status

• Traffic density
Exposure Assessment Using GIS

- Mother’s residential address at birth geocoded to lat/long for 91 cases (99%) and 360 controls (98%)

- Socioeconomic characteristics from the 1990 census for block groups

- Average Daily Traffic (ADT) for 1993 (1:24,000 scale street network layer)
Percent of Case Children with the Same Address: Birth to Diagnosis

Reynolds et. al., Bioelectricmagnetics 2001
Residential Stability by SES:
San Diego Pilot Study

Reynolds et. al., Bioelectric magnetics 2001

\[ p=0.03 \]
Residential Stability by Traffic Density: Total ADT

Percent with Same Address

Total Average Daily Traffic

Total | High | Medium | Low

p=0.29

Reynolds et. al., Bioelectricmagnetics 2001
Residential Mobility in the Northern California Childhood Leukemia Study (NCCLS)

- Cases (n=380):
  - 1997-1999 leukemia diagnoses under the age of 15 in 35 northern California counties

- Detailed residential history collected via interview

- Addresses geocoded to a lat/long

- Urbanization and SES metrics from 1990 and 2000 census data
Number of Residences for Case Children: NCCLS Study

Urayama et. al., Ann. Epidemiol 2009
Residential Mobility among Case Children: NCCLS Study

- Mother moved B4 birth
- Moved during first year of life
- Out of county of birth
- Out of CA 1+ times

Urayama et. al., Ann. Epidemiol 2009
Concordance of Birth vs. Diagnosis Block
Group SES: NCCLS Study

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<thead>
<tr>
<th>Diagnosis Residence</th>
<th>Low SES</th>
<th>Medium SES</th>
<th>High SES</th>
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<tr>
<td>Low SES</td>
<td>62%</td>
<td>16.7%</td>
<td>2.3%</td>
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<tr>
<td>Medium SES</td>
<td>32%</td>
<td>62%</td>
<td>25.6%</td>
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<tr>
<td>High SES</td>
<td>6%</td>
<td>21.3%</td>
<td>72.1%</td>
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</table>

Urayama et. al., Ann. Epidemiol 2009
Concordance of Birth vs. Diagnosis Block
Group Urbanization: NCCLS Study

<table>
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<tr>
<th>Diagnosis Residence</th>
<th>Birth Residence</th>
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<tr>
<td>Rural</td>
<td>Rural</td>
<td>86.7%</td>
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<td>City</td>
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<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60.2%</td>
</tr>
</tbody>
</table>

Urayama et. al., Ann. Epidemiol 2009
Odds Ratios and 95% CI for childhood leukemia at the 75th percentile of residential ADT in the NCCLS study.

Von Behren, et.al., CEBP, 2008
Findings for Childhood Leukemia

• High residential mobility even among very young children
  • Usually only address information for one or two points in time
  • Difficulties in assigning exposures from environmental agents
  • Birth address may not be a good indicator of in utero exposures

• Residential mobility non-random
  • Differences by SES
  • Differences by residential ADT

• Some suggestion of windows of susceptibility, particularly:
  • In utero
  • For cumulative exposures in early life
  • Recent exposures
  • Not necessarily time to event
Breast Cancer
Latency/windows of susceptibility

• Breast cancer is a very heterogeneous disease

• Risk relationships differ by
  • Age at onset (premenopausal vs. postmenopausal)
  • Cell type (ductal vs. lobular)
  • Hormone receptor status (ER/PR)

• Some potentially key windows of susceptibility to environmental exposures:
  • In utero exposures
  • Early life
  • Adolescence
  • Prior to a first full term pregnancy
  • Recent exposures
  • Lifetime cumulative exposures
Clues for windows of susceptibility for breast cancer

• *In utero*
  • Birth characteristics (eg. high birth weight, older maternal age)

• Puberty
  • Ionizing radiation
  • DDT/DDE
  • NIEHS Centers for Breast Cancer and the Environment

• Prior to a first pregnancy
  • Active smoking

• Recent
  • Breast cancer rates post-WHI
For GIS Studies What Address is Best?

• When is the biologically important time window of risk?

• Where do women spend the most time?

• Is residential mobility different by:
  - Demographic characteristics?
    • e.g. SES status?
California Teachers Study - Overview

- Funded with breast cancer tobacco tax $
- Mailing to female STRS members in 1995
- Statewide cohort (133,479)
- Annual re-contact/biennial questionnaire
- Outcome follow-up via linkage to CCR/vital records
- Largest prospective study specifically designed to study breast cancer
Residential Mobility in the California Teachers Study

• Sample of 328 participants
  • Balanced on urban/rural residences

• Detailed residential history information via interview
  • All addresses for residences of 6 months or longer
  • Move dates -- in and out

• Geocoded addresses for previous 10 years to lat/long
Number of Lifetime Residences among CTS Participants

Average number of residences = 8.9

Years at Current Residence among CTS Participants

Average years at current residence = 15.1

Residential Mobility among CTS Participants in Previous 10 years

Predictors of Residential Stability
(number of years at current residence)

• Age:
  • OR for age 65+ (vs. <44)=3.7 (95% CI 2.7-5.0)

• Birthplace:
  • OR for California-born (vs. other US)=1.2 (95% CI 1.02-1.4)

• SES:
  • Highest quartile (vs. lowest)=1.3 (95% CI 1.04-1.5)

(none of these predicted number of residences)

Findings for Breast Cancer Studies

• Older adults less residentially mobile

• Residential mobility non-random
  • Differences by age
  • Differences by birthplace
  • Differences by SES

• Current residence may be relevant for short latency exposures (HT model)

• Recent residential history may not be useful for early life exposures (DDT/DDE model)
Summary

• Residential location important for studies of the physical environment
  • Difficult to obtain detailed lifetime residential histories

• Residential mobility non-random
  • Importance of age, SES, other factors

• Windows of susceptibility differ by agent(s) of interest and type of cancer
  • Increasing work in this area

• More research is needed. . .