NCI Cohort and Consortial Studies

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Division of Cancer Epidemiology and Genetics
Overview

- General Cohorts
  - PLCO, Sister Study
  - Special Exposure Cohorts
  - Cancer Focus

- Current Cohorts

- Consortia
  - NCI Cohort Consortium
  - Cf. Heart Disease
  - Cf. Case-Control

- New Cohorts
  - One or more new cohorts
  - Special exposure cohorts
  - Bridging
Cohorts with Biospecimens
PLASMA ORGANOCHLORINE LEVELS AND THE RISK OF BREAST CANCER


ABSTRACT

Background Exposure to “environmental estrogens” such as organochlorines in pesticides and industrial chemicals has been proposed as a cause of increasing rates of breast cancer. Several studies have reported higher blood levels of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and polychlorinated biphenyls (PCBs) in patients with breast cancer than in controls.

Methods We measured plasma levels of DDE and PCBs prospectively among 240 women who gave a blood sample in 1989 or 1990 and who were subsequently given a diagnosis of breast cancer before June 1, 1992. We compared these levels with those measured in matched control women in whom breast cancer did not develop. Data on DDE were available for 236 pairs, and data on PCBs were available for 230 pairs.

Results The median level of DDE was lower among case patients than among controls (4.71 vs. 5.35 parts per billion, P = 0.14), as was the median level of PCBs (4.49 vs. 4.68 parts per billion, P = 0.72). The multi-

THE fivefold variation in the rates of breast cancer around the world, combined with the observation that the daughters of women who migrate from a country with a low incidence of breast cancer to a country with a high incidence acquire the breast-cancer risk prevailing in the high-incidence country, strongly suggests that environmental and lifestyle factors are the major causes of breast cancer. The incidence of breast cancer in the United States has risen by 1 percent per year since 1940, and there is uncertainty about the extent to which established risk factors can explain the increase. Environmental pollutants have been suggested as potential causes. The hypothesis that among these pollutants, hormonally active organochlorine chemicals may be responsible has garnered wide attention. Many pesticides and industrial chemicals have the potential to act as “environmental estrogens” and have been shown to affect wildlife adversely. The most abun-
Levels of metabolites of organophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa)

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Genetically Elevated C-Reactive Protein and Ischemic Vascular Disease

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ABSTRACT

BACKGROUND
Elevated levels of C-reactive protein (CRP) are associated with increased risks of ischemic heart disease and ischemic cerebrovascular disease. We tested whether this is a causal association.

METHODS
We studied 10,276 persons from a general population cohort, including 1786 in whom ischemic heart disease developed and 741 in whom ischemic cerebrovascular disease developed. We examined another 31,992 persons from a cross-sectional general population study, of whom 2521 had ischemic heart disease and 1483 had ischemic cerebrovascular disease. Finally, we compared 2236 patients with ischemic heart disease with 4474 control subjects and 612 patients with ischemic cerebrovascular disease with 1224 control subjects. We measured levels of high-sensitivity CRP and conducted genotyping for four CRP polymorphisms and two apolipoprotein E polymorphisms.

RESULTS

From the Department of Clinical Biochemistry (J.Z., B.G.N.) and the Copenhagen General Population Study (J.Z., A.T.H., J.S.J., B.G.N.); Herlev Hospital; the Department of Clinical Biochemistry (A.T.H.); Cardiology (P.G.), and Vascular Surgery (H.S.), Rigshospitalet, the Copenhagen City Heart Study, Bispebjerg Hospital (A.T.H., J.S.J., B.G.N.); and the Department of Cardiology, Gentofte Hospital (J.S.J.) — all at Copenhagen University Hospital, Faculty of Health Sciences, University of Copenhagen, Copenhagen. Address reprint requests to Dr. Nordestgaard at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark, or at bmo@hef.regionh.dk.

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The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO):

A resource for studies of cancer etiology and early disease markers

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Division of Cancer Epidemiology and Genetics
National Cancer Institute
PLCO: Randomized Clinical Trial -> Observational Cohort

- A randomized controlled trial evaluating whether selected screening tests reduce deaths due to four cancers (vs. usual care)

<table>
<thead>
<tr>
<th>Site</th>
<th>Test</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>PSA &amp; DRE</td>
</tr>
<tr>
<td>Lung</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>Flexible sigmoidoscopy</td>
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<tr>
<td>Ovary</td>
<td>CA125 &amp; TVU</td>
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</tbody>
</table>
PLCO Study Population

- 155,000 men and women aged 55-74 at enrollment with no history of P, L, C or O cancers
  - 90% non-Hispanic Caucasian, 50% female


- Screening arm: 6 annual medical examinations

- 13 years of annual active follow-up (to be extended)
PLCO: Resource for Molecular Epidemiologic Research

• PLCO designed to develop a rich biospecimen repository for molecular epidemiologic studies of cancer etiology and early disease detection

• Available for use by intramural and extramural investigators (contingent upon approval by scientific review panel)

• Detailed info at www.plcostars.com
# Biospecimens Collected in PLCO

<table>
<thead>
<tr>
<th>Screening Visit</th>
<th>Serum</th>
<th>Plasma</th>
<th>Buffy Coat</th>
<th>RBC</th>
<th>Whole Blood</th>
<th>Buccal Cell</th>
<th>Tumour Tissue</th>
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<tr>
<td>Baseline</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Year 1</td>
<td>X</td>
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<tr>
<td>Year 2</td>
<td>X</td>
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<tr>
<td>Year 3</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Year 4</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Year 5</td>
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<td>X</td>
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<td>X</td>
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<td>2004-2008</td>
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<td>X</td>
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**Control Arm**

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<tbody>
<tr>
<td></td>
<td>X</td>
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</tbody>
</table>
PLCO Blood Specimens

• Collected from screening-arm participants (N=66,000)

• Collected on-site at screening centers with immediate processing under a uniform protocol into stored components:
  – Serum
  – Plasma-heparin & plasma-EDTA
  – Buffy coat
  – Red blood cells
  – Cryopreserved whole blood

• Serially collected serum & plasma ideal for validating potential markers of early disease
PLCO Buccal Cell Specimens

- Collected from control-arm participants
- Mailed collection kit using mouthwash
- DNA (from blood or buccal cells) available for 113,000 participants
PLCO Questionnaires & Clinical Data

– Baseline and supplemental risk factor questionnaires (smoking, family history, comorbidities, anthropometry, medication use, hormone therapy, others)

– Dietary food frequency questionnaires

– Screening data

– Treatment data (P, L, C, O only)

– Previously collected biochemical & genetic data
Using PLCO Resources

www.PLCOstars.com

Learn more

• Background on Trial and biospecimen collection methods

• Copies of all study questionnaires

• Numbers of accrued cancers with biospecimens

Apply to use

• Data-only study proposals
  – accepted continuously
  – reviewed at PLCO Sub-Committee meeting (every 3-4 months)

• Biospecimen-based study proposals
  – the Etiology and Early Marker Studies program (EEMS) accepts proposals twice per year (Jan 15 & June 30)
  – Reviewed and scored by review panel of investigators from NCI, screening centers and extramural community
Biospecimen Project Examples

**Approved**

- Organochlorine compounds and PBDEs
  - Thyroid cancer C-C study.
  - Controversial
  - Large volume of serum (~0.7ml)
- Plasma NNA and NNK (metabolites of tobacco smoke)
  - Lung cancer study C-C
  - Volume also pretty high (1.0ml)
- Vitamin D and six rare cancers
- Cytokine panel (small volume)
- Various genetic scans

**Not Approved Yet**

- Plasma hormones and ovarian cancer
  - Volume
  - Ovarian cancer trial cases uniquely precious
- Various screening markers
  - Not validated yet
- Metabolomic panel
  - Pancreatic cancer
  - Under review
Sister Study Cohort: 50,000 sisters of women who have had breast cancer

- Age 35-74
- Never had breast cancer
- Volunteers - US and Puerto Rico
  - Multiple recruitment strategies
    - Media (free and paid)
    - Community and organizational partnerships
    - Sister Study participants
  - Emphasis on underrepresented groups
    - African Americans, Latinas, lower education
Sister Study Design

Enroll 50,000

Recruit Volunteers

Phone Screen

Web Screen

Home Visit

Bank Samples

Annual Follow-up

Biennial Questionnaire

Random Sample

Cases

Confirm Diagnosis

Phone Interviews
## Sample Collection

<table>
<thead>
<tr>
<th>Type</th>
<th>% with sample</th>
<th>Biological specimen inventory System</th>
</tr>
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<tbody>
<tr>
<td>Blood</td>
<td>99.2</td>
<td>Extensive QA/QC</td>
</tr>
<tr>
<td>Urine</td>
<td>99.7</td>
<td>Anonymous samples</td>
</tr>
<tr>
<td>Dust</td>
<td>98.9</td>
<td>– Analyte degradation</td>
</tr>
<tr>
<td>Toenails</td>
<td>97.7</td>
<td>– Freeze/thaw and storage effects</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>11.7</td>
<td>– Pooled and individual samples for assay/Lab controls, assay development</td>
</tr>
<tr>
<td>Saliva</td>
<td>0.4</td>
<td>– Intra- and inter-individual variation, seasonal effects</td>
</tr>
</tbody>
</table>
Follow-Up Response Rates

First annual update (31,090 women)
- Response rate 95.5%, most respond with little prompting
- Added phone data collection for minorities and lower education
  - Response rates 95.7% - 97.9% response

Second update - 95.7% response

First biennial (11,243 women) - 95.3%

Cohort communication to maintain high response
Lifetime Influences on Women’s Health

Birthweight
Family history
Maternal pregnancy

Puberty timing

Early menopause
Fibroids
Infertility
Menstruation
Pregnancies

Autoimmune diseases
Migraines
Thyroid disease

Breast cancer
Cardiovascular disease
Diabetes
Obesity
Other cancers

Cognitive decline
Neurodegenerative disease
Osteoporosis
Stroke

Prenatal  Childhood  Teens  Reproductive Years  Peri-menopause  Post-Menopause  Elderly Years

Menopause

Estrogens/Progestins

Exposure
Examples: BPA versus Phthalates

- Stable over time? Or at least rank stable?
- Assays reliable?
- Right component available, e.g., urine?
- Volume available?
- Competing uses?
- Less valuable alternative resources to test?
- Pilot work first: BPA: No, Phthalates: Yes
The Problem: Numbers Run Out
The Solution: Cohort Consortium
NCI Cohort Consortium Aims

Communication

Solve Common Problems

Collaborations

Signature Projects
NCI Cohort Consortium 2010

• 40 Member Cohorts
  – Defined cohort of 10,000 participants
  – Risk factors measured at baseline or later
  – Cancers accurately ascertained

• Signature Projects
  – BPC3, CGEMS, PanScan: Scanning for genetic risk
  – Vitamin D in pre-diagnostic serum
  – BMI and mortality in very large study
Limitations of Individual Cohorts: Numbers Exposed or Affected
NHL Risk with Low Vitamin D

Males, 25 (OH)D <25 nmol/L compared with the referent (50−<75 nmol/L)
NHL Risk with High Vitamin D

Males, 25 (OH)D 100+ nmol/L compared with the referent (50–<75 nmol/L)
There are other places to look...
The Asia Cohort Consortium

The Asia Cohort Consortium (ACC) is a collaborative effort seeking to understand the relationship between genetics, environmental exposures, and the etiology of disease through the establishment of a cohort of at least one million healthy people around the world.
Exposure-Risk Scanning: Using Cohorts and Consortia

• Current research is strong and will continue
  – Little metabolomics now
  – Large scale coming

• We face big challenges
  – Uncertain time course of exposure measures
  – Often big volume requirements
  – Often need testing and proving assay
  – Uncommon or uncertain outcomes
Exposure-Risk Scanning: What To Do Next

• Develop high throughput techniques
• Start with panels of related metabolites
• Combine cohort, case-control and pilot studies
• Accept that small volume studies will continue
• Concentrate on persistent exposures
• Encourage multi-outcome studies
What cohorts do we need?
Emerging Ideas

What Does the Optimal Cohort Study Look Like?

- Large in scale, diverse (≥500k)
- Address multiple diseases/risk factors
- Highly efficient recruitment, data collection, sample processing
- Linked personal electronic records
- High sample and data quality
- State-of-the-art technology
- Cost effective
- Data available for qualified researchers

Courtesy Teri Manolio 2/2010
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