The Genetic Component of a Common Disease

The Paradigm of Cancer Genetics

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Goal

☐ Understand how genetics fits
  ■ Case study approach – breast cancer

2 Key Frameworks

☐ Is this a public health problem?
  ■ What is the genetic component?
☐ Is this a “good” genetic test? (ACCE)

Case Study

☐ Your neighbor and two of her daughters have had breast cancer. A gentleman across the street died from lung cancer last year, and a young girl next door to him was just diagnosed with leukemia.
☐ Is there a “true” cluster of cancer on your street (i.e., public health concern)?
☐ What do you want to know?

Is this a cancer cluster?

☐ “a greater-than-expected number of cancer cases that occurs within a group of people in a geographic area over a period of time” http://www.cdc.gov/nceh/clusters/

Long Island Breast Cancer Study

What questions would you ask?
Behavior
Genetics
Environment
Healthcare
Social Circumstances

McGinnis JM et al. Health Aff 2002;21(2):78-93

Environment?

How would you investigate?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases (n=1,596)</th>
<th>Controls (n=1,596)</th>
<th>Aggregated OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of cancer</td>
<td>1196</td>
<td>79.3</td>
<td>87.0</td>
</tr>
<tr>
<td>Expt Agng</td>
<td>293</td>
<td>19.2</td>
<td>19.7</td>
</tr>
<tr>
<td>Missing</td>
<td>47</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

Is this a cancer cluster?

- "a greater-than-expected number of cancer cases that occurs within a group of people in a geographic area over a period of time" http://www.cdc.gov/nceh/clusters/
- "More cases of a specific type(s) of cancer within a family than statistically expected..." J Genet Couns 2007;16:241-260

Substantial public health burden?

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1 in 19</td>
</tr>
<tr>
<td>Urinary bladder†</td>
<td>1 in 87</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 55</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 in 73</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 95</td>
</tr>
</tbody>
</table>

*For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2001-2003.


Lifetime Probability of Developing Cancer, by Site, Women, 2001-2003"
Major characteristics of hereditary cancer

- Multiple close family members
- Early-onset
- Rare cancers
- Multiple cancers in the same person
- Syndromic appearance

Accurately reported by family members?

- 822 Women’s Health clinic patients whose mothers did not have breast cancer
- 16% of participants reported a maternal relative with breast cancer
- 10% reported a paternal relative
### Is Family History Reporting Valid?

<table>
<thead>
<tr>
<th>Type of Relative</th>
<th>Frequency (n)</th>
<th>%</th>
<th>Error Rate (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>20</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>40</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>40</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>10</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ziogas et al., Am J Prev Med 2003;24(2):190-8*

### Effective interventions for primary and secondary prevention?

- **Family History**
- **Screening**
- **Risk Reducing Surgery**
- **Chemo-Prevention**
- **Lifestyle Changes**

### But most is not familial
- Could still be genetic
- This is the genomic era

### Do we still need family history?

- **Unknown Genes with Variable Associated Risk**: 4%
- **BRCA1**: 20%
- **BRCA2**: 20%
- **TP53**: 4%
- **CHEK2**: 5%

*N Engl J Med 2003;348:2339-47*

### Is this a “good” genetic test?

**ACCE Framework**

*http://www.cdc.gov/genomics/gtex/ACCE.htm*
What would you recommend?

☐ Your neighbor and two of her daughters have had breast cancer. A gentleman across the street died from lung cancer last year, and a young girl next door to him was just diagnosed with leukemia.
☐ Is this a public health concern?
☐ What “test” would you recommend?