THE RISK OF CHILDHOOD CANCER WITH SYMPTOMS/SIGNS PRESENTING IN PRIMARY CARE IN THE UK: A POPULATION-BASED CASE-CONTROL STUDY

Rachel Dommett(1) Theresa Redaniel(2) Richard Martin(2) Willie Hamilton(3) Michael Stevens(4)

(1) University of Bristol, Paediatric Oncology, Bristol, UK
(2) University of Bristol, School of Social and Community Medicine, Bristol, UK
(3) University of Exeter, Primary Care Diagnostics, Exeter, UK
(4) Paediatric Oncology, Bristol Royal Hospital for Children, Bristol, UK

Diagnostic journey

- Biological onset of disease
- Symptom onset
- Seek medical attention
- Doctor recognises cancer as a possibility
- Investigation - Diagnosis - Treatment

Time to Diagnosis

Patient

Doctor
Referral guidelines for suspected cancer

- Published March 2000, Updated June 2005

- Immediate referral
  e.g. unexplained petechiae, hepatosplenomegaly

- Urgent referral
  e.g. repeat attendance, same problem, no clear diagnosis

- Refer
  e.g. rest pain, back pain and unexplained lump

Features of childhood cancer in primary care: a population-based nested case-control study
Br J Cancer. 2012 Feb 28;106(5):982-7

- NICE alert symptoms and frequent consultations are associated with childhood cancer in primary care

- Although the predictive value of individual symptoms and consultation frequency is low they do alter the prior probability of cancer
Aim

- to identify pre-diagnostic symptoms and signs strongly related to the subsequent diagnosis of childhood cancer

Methods

- Population-based nested case-control study
- Historical cohort, data collected prospectively

GPRD

- World's largest computerised database of anonymised longitudinal medical records from primary care
- >600 primary care practices throughout the UK
- Covers ~8% of the population
- 62 million patient years of high quality validated data
Study population

- 0-14 years
- Data collected in GPRD 1988-2010

- Cases & Controls (n = 1,267 vs. 15,318)
  - matched on age, sex and practice

Symptom libraries

- representing symptoms/signs (not just alert symptoms)
- control conditions - head lice and acne

Outcome measures

- Likelihood ratio (LR)
  - chance of a patient with cancer having a symptom ÷
  chance of a patient without cancer having the same symptom

- Positive predictive value (PPV)
  - the chance of a patient having cancer when they have reported
    the symptom
  - posterior odds = prior odds × LR
Identification of independent associations with cancer

- Univariable analysis

  - Selected features of cancer which were all more common in cases than controls ($p < 0.001$)

  - Control conditions, head lice and acne ($p = 0.2$)
Multivariable analyses

• Identified all candidate symptoms / signs from univariable analysis occurring in at least 2% cases with p<0.01 (n=24)

• 16 variables remained in the final model using threshold of p<0.01

• 12 variables had a PPV ≥0.04% (i.e. 10 fold increase compared to a background probability of cancer in a 3 month period of 0.0035%)
<table>
<thead>
<tr>
<th>Symptom / Sign</th>
<th>Cases N=1,267</th>
<th>Control N=15,318</th>
<th>Odds Ratio[^1]</th>
<th>Positive Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freq</td>
<td>%</td>
<td>Freq</td>
<td>%</td>
</tr>
<tr>
<td>Pallor</td>
<td>29</td>
<td>2.3</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>Lump Mass Swelling head and neck</td>
<td>28</td>
<td>2.2</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Lump Mass Swelling[^2]</td>
<td>42</td>
<td>3.3</td>
<td>16</td>
<td>0.1</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>69</td>
<td>5.5</td>
<td>33</td>
<td>0.2</td>
</tr>
<tr>
<td>Abnormal movement</td>
<td>49</td>
<td>3.9</td>
<td>26</td>
<td>0.2</td>
</tr>
<tr>
<td>Bruising</td>
<td>33</td>
<td>2.6</td>
<td>18</td>
<td>0.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42</td>
<td>3.3</td>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>28</td>
<td>2.2</td>
<td>21</td>
<td>0.1</td>
</tr>
<tr>
<td>Headache</td>
<td>73</td>
<td>5.8</td>
<td>55</td>
<td>0.4</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>28</td>
<td>2.2</td>
<td>21</td>
<td>0.1</td>
</tr>
<tr>
<td>Pain</td>
<td>42</td>
<td>3.3</td>
<td>41</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>107</td>
<td>8.5</td>
<td>102</td>
<td>0.7</td>
</tr>
</tbody>
</table>

[^1] Symptoms are ordered by Positive Predictive Value
[^2] adjusted for all the symptoms appearing in the table
[^3] Lump Mass Swelling below neck excluding abdomen
Highest PPV was for pallor: for children with this sign, the prior probability of childhood cancer changes from approximately 0.35 per 10,000 (the background incidence for a 3 month period) to 41 in 10,000 (i.e. 0.41%).

Four symptoms were associated with PPVs of 0.09% or greater, increasing the risk to at least a 10 in 10,000 likelihood of cancer.
E.g. of 10,000 children attending GP with visual symptoms within a 3 month period, 6 would be diagnosed with cancer but if also seen > twice (for any reason), number diagnosed with cancer would increase to 23 (almost 4 fold difference)

<table>
<thead>
<tr>
<th>Symptom / Sign</th>
<th>PPV as a single variable</th>
<th>PPV combined with 3 or more consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>0.41</td>
<td>0.76</td>
</tr>
<tr>
<td>Lump Mass Swelling head and neck</td>
<td>0.30</td>
<td>0.76</td>
</tr>
<tr>
<td>Lump Mass Swelling</td>
<td>0.11</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0.09</td>
<td>0.2</td>
</tr>
<tr>
<td>Abnormal movement</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>Bruising</td>
<td>0.08</td>
<td>0.38</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>Headache</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>0.06</td>
<td>0.23</td>
</tr>
<tr>
<td>Pain</td>
<td>0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>0.04</td>
<td>0.13</td>
</tr>
<tr>
<td>3 or more consultations</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

I.e. 76 cases/10,000 against a background risk of 0.35/10,000
Conclusions

• We identified 12 symptoms which alter the prior probability of a cancer diagnosis from ~1 in 10,000/year to at least 1 in 1000

• PPVs were higher when a child had presented multiple times in a 3 month period

• Symptoms and consultation frequency could be integrated into GP computer systems

Acknowledgements