

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

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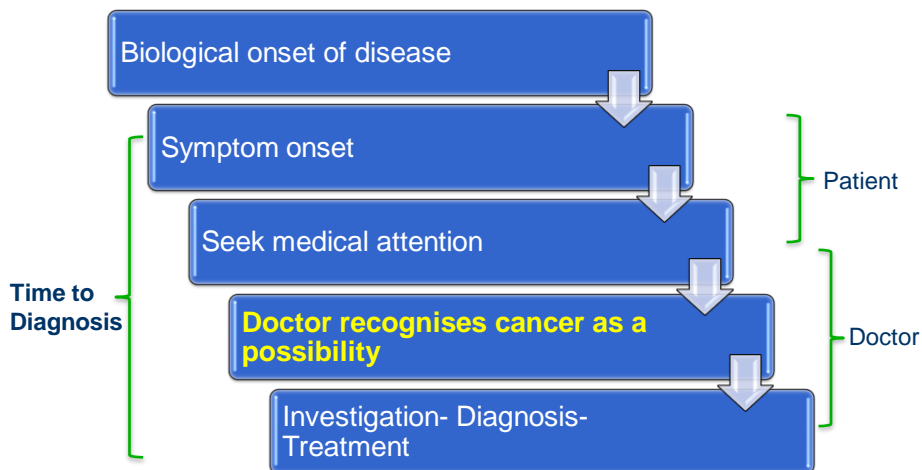
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Diagnostic journey





National Institute for
Health and Clinical Excellence

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

More than *just* a database

- 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

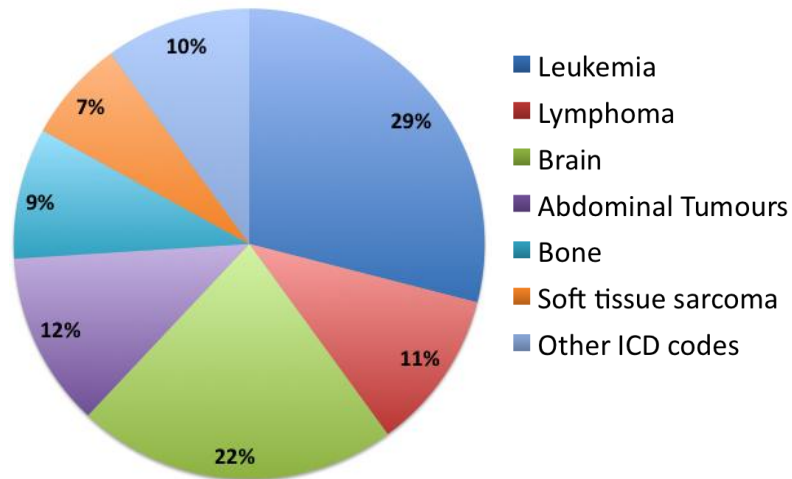
- representing symptoms/signs (not just alert symptoms)
- control conditions- head lice and acne

🌟 Outcome measures

- **Likelihood ratio (LR)**
 - chance of a patient with cancer having a symptom \div
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 \times LR

Case distribution



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 ($p = 0.2$)

Symptom / Sign *	Cases N=1,267		Control N=15,318		Likelihood ratio	95% CI
	Freq	%	Freq	%		
	3 or more consultations	575	45.4	1240		
Upper Respiratory Tract Infection (URTI)	143	11.3	942	6.2	1.8	1.6-2.2
Musculoskeletal symptoms	107	8.5	102	0.7	12.7	9.7-16.5
Vomiting	86	6.8	105	0.7	9.9	7.5-13.1
Cough	77	6.1	654	4.3	1.4	1.1-1.8
Headache	73	5.8	55	0.4	16.1	11.4-22.7
Lymphadenopathy	69	5.5	33	0.2	25.3	16.8-38.1
Rash	63	5.0	555	3.6	1.4	1.1-1.8
Abdominal pain	60	4.7	137	0.9	5.3	3.9-7.1
Childhood infection	54	4.3	236	1.5	2.8	2.1-3.7
Fever	49	3.9	166	1.1	3.6	2.6-4.9
Abnormal movement	49	3.9	26	0.2	22.8	14.2-36.5
Abdominal mass	48	3.8	0	0.0		
Pain	42	3.3	41	0.3	12.4	8.1-19.0
Fatigue	42	3.3	24	0.2	21.2	12.9-34.8
Lump Mass Swelling (below neck exc. abdo)	42	3.3	16	0.1	31.7	17.9-56.3
Eye swelling	39	3.1	238	1.6	2.0	1.4-2.8
Shortness of breath	35	2.8	221	1.4	1.9	1.4-2.7
Bruising	33	2.6	18	0.1	22.2	12.5-39.3
Pallor	29	2.3	3	0.0	116.9	35.7-383.1
Bleeding	28	2.2	21	0.1	16.1	9.2-28.3
Lump Mass Swelling of head and neck	28	2.2	4	0.0	84.6	29.7-240.9
Visual symptoms	28	2.2	21	0.1	16.1	9.2-28.3
Constipation	26	2.1	61	0.4	5.2	3.3-8.1

* Ordered by frequency in the 3 months prior to index date in the cases

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 $\geq 0.04\%$ (i.e. 10 fold increase compared to a background probability of cancer in a 3 month period of 0.0035%)

Symptom / Sign *	Cases		Control		Odds Ratio ¹	Positive Predictive Value (%)
	N=1,267		N=15,318			
	Freq	%	Freq	%		
Pallor	29	2.3	3	0.02	83.7	0.41
Lump Mass Swelling head and neck	28	2.2	4	0.03	16.9	0.30
Lump Mass Swelling ²	42	3.3	16	0.1	21.8	0.11
Lymphadenopathy	69	5.5	33	0.2	10.1	0.09
Abnormal movement	49	3.9	26	0.2	16.4	0.08
Bruising	33	2.6	18	0.1	12.3	0.08
Fatigue	42	3.3	24	0.2	7.7	0.07
Bleeding	28	2.2	21	0.1	9.9	0.06
Headache	73	5.8	55	0.4	6.1	0.06
Visual symptoms	28	2.2	21	0.1	10.4	0.06
Pain	42	3.3	41	0.3	7.3	0.04
Musculoskeletal symptoms	107	8.5	102	0.7	5.3	0.04

* Symptoms are ordered by Positive Predictive Value
¹adjusted for all the symptoms appearing in the table
²Lump Mass Swelling below neck excluding abdomen

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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%).

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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.

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

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Abnormal movement	0.08	0.15
Bruising	0.08	0.38
Fatigue	0.07	0.12
Bleeding	0.06	0.11
Headache	0.06	0.13
Visual symptoms	0.06	0.23
Pain	0.04	0.14
Musculoskeletal symptoms	0.04	0.13
3 or more consultations	0.02	

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

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)

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

