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Risk of childhood cancer with symptoms in primary care:

a population-based case-control study

Abstract

Background
Guidelines describing symptoms in children that should alert GPs to consider cancer have been developed, but without any supporting primary-care research.

Aim
To identify symptoms and signs in primary care that strongly increase the likelihood of childhood cancer, to assist GPs in selection of children for investigation.

Design and setting
A population-based case-control study in UK general practice.

Method
Using electronic primary care records from the UK General Practice Research Database, 1267 children aged 0–14 years diagnosed with childhood cancer were matched to 15 318 controls. Clinical features associated with subsequent diagnosis of cancer were identified using conditional logistic regression, and likelihood ratios and positive predictive values (PPVs) were estimated for each.

Results
Twelve symptoms were associated with PPVs of ≥0.04%, which represents a greater than tenfold increase in prior probability. The six symptoms with the highest PPVs were pallor (odds ratio, OR = 84; PPV = 0.41% (95% confidence interval [CI] = 0.12% to 1.34%), head and neck masses (OR = 17; PPV = 0.30%; 95% CI = 0.10% to 0.84%), masses elsewhere (OR = 22; PPV = 0.11%; 95% CI = 0.06% to 0.20%), lymphadenopathy (OR = 10; PPV = 0.09%; 95% CI = 0.06% to 0.13%), symptoms/signs of abnormal movement (OR = 16; PPV = 0.08%; 95% CI = 0.04% to 0.14%), and bruising (OR = 12; PPV = 0·08%; 95% CI = 0.05% to 0.13%). When each of these 12 symptoms was combined singly with at least three consultations in a 3-month period, the probability of cancer was between 11 and 76 in 10 000.

Conclusion
Twelve features of childhood cancers were identified, each of which increased the risk of cancer at least tenfold. These symptoms, particularly when combined with multiple consultations, warrant careful evaluation in general practice.

Keywords
cancer, child; diagnosis; primary health care.

INTRODUCTION

Although cancer in children is rare, with an annual incidence among 0–14 year olds in the UK of just under 1.4 per 10 000, it is the leading cause of disease-related death in children.[1] Diagnostic delays may contribute to poorer cancer outcomes in the UK when compared to other European countries, including for childhood tumours.[2,3] Early diagnosis is highlighted in the UK Cancer Reform Strategy.[4,5] Diagnostic delays also influence patient and parent experiences, reducing their confidence in the healthcare system.[2,6,7]

Diagnosis of cancer in a child is a once-in-a career event for the average GP in the UK, making it impossible for a GP to build up sufficient experience to be confident in recognising paediatric cancer. Nevertheless, GPs generally become highly experienced in identifying the seriously ill child, even if the specific diagnosis may not be apparent. The National Institute for Health and Clinical Excellence (NICE) guidelines for investigation of suspected cancer describe symptoms in children that should alert GPs to consider cancer seriously.[8] However, these guidelines were developed in the absence of a specific evidence base and without any supporting primary care research in children, and thus largely describe symptoms deemed pathognomonic of cancer at the time of diagnosis in tertiary care. They are currently being updated (2012–2014). In an earlier study, the authors confirmed an association between NICE 'alert' or 'red-flag' symptoms recorded in GPs' notes and childhood cancer.[9] However, these alert symptoms were relatively uncommon in children later diagnosed with cancer. Overall, just over one-quarter had any alert symptom recorded in the 3 months before diagnosis, and only one-third in the preceding year.[9] Alert symptoms were also recorded in those without cancer. This, coupled with the rarity of childhood cancer, meant that any individual alert symptom had a very low positive predictive value (PPV) for cancer in primary care. A recent Danish questionnaire study sent to the GPs of 253 children with cancer reported that under half of children had a symptom specifically pointing to a cancer.[10]

This current study was designed to identify prediagnostic symptoms and signs (not just 'alert' symptoms) within primary care, strongly related to childhood cancer, which could assist GPs in selection of patients for investigation of possible cancer.

METHOD

Study design

This was a population-based case-control study using the UK General Practice Research Database (GPRD; now called Clinical Practice Research Datalink). The GPRD is a prospectively gathered, anonymised, database holding administrative, clinical and prescribing records for 11 million patients, from over

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How this fits in

Guidelines describing symptoms in children that should alert GPs to consider cancer have been developed, but without any supporting primary-care research. This study identified 12 features of childhood cancers, each of which increased the risk of cancer at least tenfold. These symptoms, particularly when combined with multiple consultations, warrant careful evaluation in general practice. These data may offer the basis for an automated alert system within primary care computing systems.

600 general practices across the UK (approximately 8% of the population).[11]

Individuals in the database are representative of the UK population in terms of age, sex, and geographical distribution.[12] Data are subject to thorough validation,[13,14] audit, and quality checks, and have been used in >800 peer-reviewed publications, including studies of the symptoms of colorectal,[15–17] and brain tumours,[18] and alarm symptoms in adult cancers.[19]

Study population

Cases were all children aged 0–14 years, inclusive, with cancers diagnosed between 1 January 1988 and 31 December 2010. The cancers were identified from predefined medical codes used to record malignancies in the electronic medical records of the GPs contributing to the GPRD (full list available from authors). Only GP practices contributing research-standard data for at least 1 year before the child's date of cancer diagnosis were included. All cases and controls were included in the analysis, irrespective of whether or not they had consulted.

Cases and controls

The date of diagnosis (index date) for cases was defined as the date of the first cancer code recorded. Up to 13 controls registered with the practice on the index date of their case and never diagnosed with cancer were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex, and practice.

Symptoms and consultations

The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. During the consultation, the GP can select any of these codes to describe the medical events. From these, and the secondary/tertiary care literature, libraries of codes were assembled, representing individual symptoms or signs of possible cancer in children. These were compiled separately by a paediatric oncologist and a GP, and differences agreed by consensus and/or discussion with a paediatric oncologist. They included all well-accepted synonyms for a symptom, so, for example, fatigue included 'tiredness'. Two conditions (head lice and acne), considered to be unrelated to cancer, were included to identify any recording bias (patients with cancer may attend more frequently, giving more opportunities for recording of a symptom). Consultations in the 3 months before diagnosis were identified. This 3-month period was a pragmatic choice based on the authors' previous research showing

Table 1. Distribution of cases and controls by cancer site, age, and sex

			By age group, frequency, %				By sex, frequency, %			
	All patients, frequency, %		0–4 years		5–14 years		Male		Female	
Cancer site	Cases, *n* = 1267	Controls, *n* = 15 318	Cases, *n* = 436	Controls, *n* = 4802	Cases, *n* = 831	Controls, *n* = 10 516	Cases, *n* = 703	Controls, *n* = 8461	Cases, *n* = 564	Controls, *n* = 6857
Leukaemia	368 (29.0)	4484 (29.3)	152 (34.9)	1763 (36.7)	216 (26.0)	2721 (25.9)	203 (28.9)	2470 (29.2)	165 (29.3)	2014 (29.4)
Brain	270 (21.3)	3304 (21.6)	73 (16.7)	817 (17.0)	197 (23.7)	2487 (23.6)	141 (20.1)	1703 (20.1)	129 (22.9)	1601 (23.3)
Lymphoma	142 (11.2)	1780 (11.6)	14 (3.2)	157 (3.3)	128 (15.4)	1623 (15.4)	92 (131)	1152 (13.6)	50 (8.9)	628 (9.2)
Bone	107 (8.4)	1360 (8.9)	6 (1.4)	77 (1.6)	101 (12.2)	1283 (12.2)	62 (8.8)	787 (9.3)	45 (8.0)	573 (8.4)
Soft tissue sarcoma	91 (7.2)	1092 (7.1)	29 (6.7)	297 (6.2)	62 (7.5)	795 (7.6)	56 (8.0)	662 (7.8)	35 (6.2)	430 (6.3)
Renal	82 (6.5)	947 (6.2)	59 (13.5)	655 (13.6)	23 (2.8)	292 (2.8)	40 (5.7)	443 (5.2)	42 (7.4)	504 (7.4)
Neuroblastoma	75 (5.9)	828 (5.4)	52 (11.9)	538 (11.2)	23 (2.8)	290 (2.8)	45 (6.4)	494 (5.8)	30 (5.3)	334 (4.9)
Other ICD codes	132 (10.4)	1523 (9.9)	51 (11.7)	498 (10.4)	81 (9.7)	1025 (9.7)	64 (9.1)	750 (8.9)	68 (12.1)	773 (11.3)
Total			436 (100)	4802 (100)	831 (100)	10 516 (100)	703 (100)	8461 (100)	564 (100)	6857 (100)

ICD-10. Classification of Mental and Behavioural Disorders. [20]

Table 2. Frequency of selected variables and likelihood ratios for all cancers

	Cases, *n* = 1267		Controls, *n* = 15 318			
Symptom[a]	**Frequency**	**%**	**Frequency**	**%**	**LR**	**95% CI**
Three or more consultations	575	45.4	1240	8.1		
Upper respiratory tract infection	143	11.3	942	6.2	1.8	1.6 to 2.2
Musculoskeletal symptoms	107	8.5	102	0.7	12.7	9.7 to 16.5
Vomiting	86	6.8	105	0.7	9.9	7.5 to 13.1
Cough	77	6.1	654	4.3	1.4	1.1 to 1.8
Headache	73	5.8	55	0.4	16.1	11.4 to 22.7
Lymphadenopathy	69	5.5	33	0.2	25.3	16.8 to 38.1
Rash	63	5.0	555	3.6	1.4	1.1 to 1.8
Abdominal pain	60	4.7	137	0.9	5.3	3.9 to 7.1
Childhood infection	54	4.3	236	1.5	2.8	2.1 to 3.7
Fever	49	3.9	166	1.1	3.6	2.6 to 4.9
Abnormal movement	49	3.9	26	0.2	22.8	14.2 to 36.5
Abdominal mass[b]	48	3.8	0	0.0	–	–
Pain	42	3.3	41	0.3	12.4	8.1 to 19.0
Fatigue	42	3.3	24	0.2	21.2	12.9 to 34.8
Lump mass swelling (below neck excluding abdomen)	42	3.3	16	0.1	31.7	17.9 to 56.3
Eye swelling	39	3.1	238	1.6	2.0	1.4 to 2.8
Shortness of breath	35	2.8	221	1.4	1.9	1.4 to 2.7
Bruising	33	2.6	18	0.1	22.2	12.5 to 39.3
Pallor	29	2.3	3	0.0	116.9	35.7 to 383.1
Bleeding	28	2.2	21	0.1	16.1	9.2 to 28.3
Lump mass swelling of head and neck	28	2.2	4	0.0	84.6	29.7 to 240.9
Visual symptoms	28	2.2	21	0.1	16.1	9.2 to 28.3
Constipation	26	2.1	61	0.4	5.2	3.3 to 8.1

[a]Ordered by frequency of symptoms in the 3 months prior to index date in the cases. All symptoms/features were more common in cases than controls (P<0.001). [b]Abdominal masses were only recorded in cases and were omitted from further analyses. LR = likelihood ratio.

significant increases in consultation rates during this time in children subsequently diagnosed with cancer.[9]

Analysis

Identification of independent associations with cancer. The main analytical method was conditional logistic regression. To manage the large quantity of data, and following recognised selection strategies,[21] only variables occurring in at least 2% of either cases or controls with a univariable *P*-value ≤0.1 entered the multivariable conditional logistic regression analyses.[22] A *P*-value of <0.01 was used for retention in the final model.

Calculation of positive predictive values. PPVs were calculated using Bayes' theorem, whereby posterior odds = prior odds × likelihood ratio.[23] The prior odds of childhood cancer were estimated from national incidence figures for 2007,[24–27] expressed as the odds of developing cancer in 3 months.

All analyses were performed using Stata (version 10).

Power calculation. Sample sizes were predetermined by the total number of cancers in the GPRD, so a power calculation was performed, using a two-sided 5% significance. Three hundred and fifty cases (for example, leukaemia) with 13 controls has >99% power to identify a change in the prevalence of a variable from 5% in controls to 10% in cases. For rarer cancers (such as neuroblastoma), 80 cases has 84% power to identify a similar change, and 97% power for a change in a more common variable from 30% in controls to 50% in cases.

RESULTS

A total of 1267 eligible cases of childhood cancer and 15 318 controls were identified. Most cases could be matched to all 13 controls, with only 64 (5%) having 7 or fewer controls. Their diagnoses, age groups, and sex are summarised in Table 1.

Identification of independent associations with cancer

Univariable analyses for selected features of cancer are shown in Table 2; all were more common in cases than controls (*P*<0.001), with the exception of the control conditions, head lice and acne (*P* = 0.2). Abdominal masses were only recorded in cases (*n* = 48) and were omitted from further analyses.

From the univariable analyses, 24 candidate variables were eligible for multivariable analyses, with 16 variables remaining in the final model. Univariable PPVs were calculated for these: 12 had a PPV of ≥0.04%, which is approximately 10 times greater than the background probability of cancer of 0.0035% in any 3-month period (Table 3).

The feature with the highest PPV was pallor (0.41%; 95% CI = 0.12% to 1.34%). Three other features had PPVs of 0.1% or greater, equating to a 1 in 1000 likelihood of cancer. These were all composite groups of lump, mass, or swelling (the GPRD codes overlap for these three features): either, neck, abdominal, or elsewhere.

Strictly, a PPV for abdominal masses cannot be calculated, as no controls had this feature, but it is clearly at least as

Table 3. Multivariable analysis of the features of childhood cancer, all cancers

	Cases, *n* = 1267		Controls, *n* = 15 318						
Symptom[a]	**Frequency**	**%**	**Frequency**	**%**	**OR[b]**	**95% CI**	***P*-value**	**PPV %**	**95% CI**
Pallor	29	2.29	3	0.02	83.7	18.0 to 390.5	<0.001	0.41	0.12 to 1.34
Lump mass swelling head and neck	28	2.21	4	0.03	16.9	5.2 to 54.9	<0.001	0.30	0.10 to 0.84
Lump mass swelling[c]	42	3.31	16	0.1	21.8	9.6 to 49.7	<0.001	0.11	0.06 to 0.20
Lymphadenopathy	69	5.45	33	0.22	10.1	5.9 to 17.4	<0.001	0.09	0.06 to 0,13
Abnormal movement	49	3.87	26	0.17	16.4	7.8 to 34.9	<0.001	0.08	0.04 to 0.14
Bruising	33	2.6	18	0.12	12.3	5.5 to 27.8	<0.001	0.08	0.05 to 0.13
Fatigue	42	3.31	24	0.16	7.7	3.8 to 15.8	<0.001	0.07	0.04 to 0.12
Bleeding	28	2.21	21	0.14	9.9	4.9 to 20.2	<0.001	0.06	0.03 to 0.10
Headache	73	5.76	55	0.36	6.1	3.8 to 9.9	<0.001	0.06	0.04 to 0.08
Visual	28	2.21	21	0.14	10.4	4.4 to 24.3	<0.001	0.06	0.03 to 0.10
Pain	42	3.31	41	0.27	7.3	4.0 to 13.4	<0.001	0.04	0.03 to 0.06
Musculoskeletal symptoms	107	8.45	102	0.67	5.3	3.6 to 7.7	<0.001	0.04	0.03 to 0.07

*[a]Symptoms are ordered by positive predictive value. [b]Adjusted for all the symptoms appearing in the table. [c]Lump mass swelling below neck excluding abdomen. OR = odds ratio. PPV = positive predict*ive value.

strong a risk as the other masses. The PPV for ≥3 consultations (for any reason) in the 3 months before diagnosis was 0.02% (95% CI = 0.02% to 0.02%). Of the whole cohort, 475 children (37.5%) had at least one of the features from Table 3, and only 80 (6.3%) had two or more features.

Table 4. Positive predictive values for individual symptoms and in combination with three or more consultations for any reason in a 3-month period (against a background risk of 0.035%)

Symptom[a]	**PPV[b] as a single variable (95% CI)**	**PPV combined with three or more consultations (95% CI)**
Pallor	0.41 (0.12 to 1.34)	0.76 (0.10 to 5.70)
Lump mass swelling head and neck	0.30 (0.10 to 0.84)	0.76 (0.10 to 5.70)
Lump mass swelling	0.11 (0.06 to 0.20)	0.30 (0.09 to 0.99)
Lymphadenopathy	0.09 (0.06 to 0.13)	0.20 (0.10 to 0.39)
Abnormal movement	0.08 (0.04 to 0.14)	0.15 (0.07 to 0.32)
Bruising	0.08 (0.05 to 0.13)	0.38 (0.09 to 1.64)
Fatigue	0.07 (0.04 to 0.12)	0.12 (0.06 to 0.23)
Bleeding	0.06 (0.03 to 0.10)	0.11 (0.04 to 0.31)
Headache	0.06 (0.04 to 0.08)	0.13 (0.08 to 0.22)
Visual symptoms	0.06 (0.03 to 0.10)	0.23 (0.07 to 0.77)
Pain	0.04 (0.03 to 0.06)	0.14 (0.07 to 0.31)
Musculoskeletal symptoms	0.04 (0.03 to 0.07)	0.13 (0.08 to 0.19)
Three or more consultations	0.02	

[a]Symptoms are ordered by PPV as a single variable. [b]Values are point estimates of the PPV. The red shading is for symptoms with a PPV over 0.1%, the blue shading is when the PPV is above 0.2%, and the purple shading is for PPVs above 0.5%. PPV = positive predictive value.

PPVs for a patient consulting a doctor in primary care

Table 4 shows the PPVs for childhood cancer for children presenting to their GP with specific clinical features, both individually and combined with a pattern of three or more consultations in the 3-month period. PPVs for multiple symptoms were generally higher, but are based on small numbers, so have not been reported here.

Analyses of specific disease groups

The cancers were combined into four disease groups: leukaemia/lymphoma, annual incidence 0.58/10 000 children; central nervous system tumours (including intracranial germ cell tumours), annual incidence 0.33/10 000; bone tumours/ soft tissue sarcoma, annual incidence 0.14/10 000; abdominal tumours (including renal, hepatic, and neuroblastoma), annual incidence 0.19/10 000), and the analyses repeated. The final multivariable models for each group are shown in Table 5. Twelve features remained in the final model for leukaemia/lymphoma, of which bruising had the highest PPV of 0.53% (95% CI = 0.07% to 3.91%). The central nervous system model contained seven features, with abnormal movement having the highest PPV of 0.11% (95% CI = 0.03% to 0.35%). Only four variables were independently associated with bone tumours and soft tissue sarcomas, all with PPVs of ≤0.1%. In the abdominal tumours group, 20% of cases (but no controls) had

Table 5. Final multivariable models for each group

	Cases, *n* = 510		Controls, *n* = 6264							
Symptom[a]	**Frequency**	**%**	**Frequency**	**%**	**OR**	**95% CI**	***P* value**	**LR**	**PPV, %**	**95% CI**
A. Leukaemia/lymphoma										
Bruising	30	5.9	1	0.02	138.1	17.6 to 1082.0	<0.001	368.5	0.53	0.07 to 3.91
Pallor	24	4.7	1	0.02	131.9	16.9 to 1031.9	<0.001	294.8	0.43	0.06 to 3.15
Lump mass swelling head and neck	20	3.9	1	0.02	59.2	7.1 to 492.6	<0.001	245.7	0.35	0.05 to 2.65
Fatigue	31	6.1	8	0.1	16.7	5.5 to 51.0	<0.001	47.6	0.07	0.03 to 0.15
Lymphadenopathy	60	11.8	17	0.3	17.9	8.8 to 36.4	<0.001	43.4	0.06	0.04 to 0.11
Lump mass swelling[b]	21	4.1	7	0.1	30.1	5.8 to 156.0	<0.001	36.9	0.05	0.02 to 0.13
Bleeding	13	2.6	7	0.1	14.7	4.1 to 52.7	<0.001	22.8	0.03	0.01 to 0.08
Pain	17	3.3	11	0.2	5.1	1.8 to 14.6	0.003	19.0	0.03	0.01 to 0.06
Musculoskeletal symptoms	45	8.8	36	0.6	5.3	2.9 to 9.5	<0.001	15.4	0.02	0.01 to 0.03
Fever	36	7.1	76	1.2	2.4	1.3 to 4.5	0.007	5.8	0.01	0.01 to 0.01
Abdominal pain	24	4.7	56	0.9	3.0	1.6 to 5.7	<0.001	5.3	0.01	0.00 to 0.01
Three or more consultations	255	50	515	8.2	4.1	3.1 to 5.6	<0.001	6.1	0.01	0.01 to 0.01
B. Central nervous system tumour										
Abnormal movement	32	11.9	3	0.1	2748.9	14.2 to 531 853.5	0.003	130.5	0.11	0.03 to 0.35
Visual symptoms	21	7.8	3	0.1	98.4	9.1 to 1067.5	<0.001	85.7	0.07	0.02 to 0.24
Vomiting	55	20.4	14	0.4	25.0	7.7 to 80.8	<0.001	48.1	0.04	0.02 to 0.07
Headache	58	21.5	18	0.5	23.0	8.3 to 63.5	<0.001	39.4	0.03	0.02 to 0.06
Pain	14	5.2	5	0.2	79.5	14.0 to 451.5	<0.001	34.3	0.03	0.01 to 0.08
Seizure[c]	10	3.7	5	0.2	15.6	1.9 to 132.2	0.010	24.5	0.02	0.01 to 0.06
Three or more consultations	137	50.7	257	7.8	4.0	2.5 to 6.7	<0.001	6.5	0.01	0.00 to 0.01
C. Bone tumour/soft tissue sarcoma										
Lump mass swelling[b]	14	7.1	2	0.1	52.2	10.1 to 270.0	<0.001	86.69	0.03	0.01 to 0.14
Musculoskeletal symptoms	42	21.2	35	1.4	6.7	3.7 to 12.3	<0.001	14.86	0.01	0.00 to 0.01
Trauma	10	5.1	32	1.3	3.9	1.5 to 10.0	0.004	3.87	0.00	0.00 to 0.00
Three or more consultations	68	34.3	141	5.8	4.1	2.7 to 6.2	<0.001	5.97	0.00	0.00 to 0.00
D. Abdominal tumour										
Bleeding	10	6.0	2	0.1	165.5	16.2	<0.001	56.14	0.03	0.01 to 0.12
Lump mass swelling[b]	5	3.0	1	0.1	62.7	4.2	0.003	56.14	0.03	0.00 to 0.23
Weight loss[c]	8	4.8	2	0.1	12.6	1.4	0.020	44.91	0.02	0.00 to 0.10
Abdominal pain	24	14.4	12	0.6	27.3	9.4	<0.001	22.46	0.01	0.01 to 0.02
Musculoskeletal symptoms	9	5.4	9	0.5	7.7	2.2	0.001	11.23	0.01	0.00 to 0.01
Childhood infection	13	7.8	40	2.1	3.8	1.6	0.003	3.65	0.00	0.00 to 0.00
Three or more consultations	81	48.5	224	12.0	3.6	2.2	<0.001	4.06	0.00	0.00 to 0.00

*[a]Symptoms are ordered by PPV. [b]Lump mass swelling below neck excluding abdomen. [c]Has a P value below the threshold but is needed in the model based on the likelihood ratio test. LR = likelihood ratio. OR = odds ratio. PPV = positive predict*ive value.

an abdominal mass or swelling. This was omitted from the multivariable modelling, as it was expected that GPs would refer all such patients. Thus the final model for children with abdominal tumours studied seven variables, omitting children with an abdominal mass.

DISCUSSION

Summary

In this study, 16 features of childhood cancer in children consulting primary care have been identified; and their risks quantified. Twelve of these symptoms increased the prior probability of childhood cancer from around 0.4 in 10 000 to at least 4 in 10 000. This tenfold increase in probability warrants consideration of cancer, although for every symptom, a benign cause remains much more likely than cancer (apart from the single exception of an abdominal mass). When these features are present in a child who attends, for any reason, for the third time in 3 months, their risk of cancer increases further. Most of the higher-risk symptoms, such as lumps or swellings, are unusual findings in clinical practice, although the significant features also include some common symptoms such as pallor and fatigue.

Strengths and limitations

This is the first study to use prospectively collected data to study all the symptoms/features of childhood cancer in UK primary care. It is large, and representative of the UK population, so the results should be generalisable to countries with strong

primary care.[11] The distribution of cancers generally matched nationally reported figures, with leukaemia the most common diagnosis overall and central nervous system tumours the most common solid tumour. The study cohort had a larger than expected number of bone tumours, most apparent, as expected, in the 5–14 years age group.[28]

Data were collected prospectively, precluding recall bias. Recording bias (when features of cancer are preferentially recorded in children who transpire to have cancer) is a theoretical possibility. There is some under-recording of symptoms in the GPRD; doctors preferring to record diagnoses where possible. However, under-recording should not affect likelihood ratios (which underpin calculation of PPVs), as long as it is consistent between cases and controls, which the authors believe is the case. The two 'control' conditions of head lice and acne were broadly similar in controls and cases, supporting this view.

Comparison with existing literature

Many of the symptoms identified in this study have been reported from secondary and tertiary care series; indeed, this literature was used in compiling the list of candidate features of cancer, before the list was broadened to include symptoms that are common in primary care.[29–33] A Danish study was conducted while this one was being carried out: although they did not report PPVs (as they had no control group), the frequency of symptoms was broadly similar to that of the present study.[10] This is encouraging, both from a methodological viewpoint, and for interpretation.

The risks of cancer with specific symptoms have not been estimated before the present study, though the authors expected them to be small. Some were not: a repeat attendance in a child with pallor or a lump/mass or swelling in the head and neck region increased the risk of cancer to 0.76%; a level that the authors believe warrants investigation. Abdominal masses were not seen in controls, but were frequent in cases, so investigation is also clearly appropriate. A childhood cancer diagnosis is rare, so PPVs will never be particularly high. However, the seriousness of paediatric cancer, coupled with the potential for cure in many, justifies investigation at a lower level of probability than would commonly be considered appropriate for adult cancers.

In the main analysis, all the common childhood cancers were grouped together. The study findings therefore represent a diverse group of diagnoses for which some symptoms are more relevant than others. This was deliberate: the aim was to identify symptoms that might highlight the possibility of cancer to a GP, rather than to list the symptoms of individual cancers. Nonetheless, once the group was subdivided into four groups of cancers, the expected symptom patterns emerged. Haematological cancers presented with bruising, pallor, lymphadenopathy, and/or fatigue.[10] Central nervous system tumours caused abnormal movements, visual disturbances, headache, and vomiting. Bone and soft tissue sarcomas presented with swellings and other musculoskeletal symptoms. Finally, abdominal tumours were characterised by abdominal masses, bleeding, weight loss and pain. These symptoms closely match reports from secondary care, and the Danish primary care study.[10,29,30,32,33]

Implications for practice

Children with unexplained bruising or pallor warrant consideration of cancer, especially if they re-attend. The word 'unexplained' is deliberate: the study methods identified consultations when the GP recorded pallor. As GPs would generally omit recording such a symptom when the cause is apparent, the results relate to the opposite clinical scenario, that is when no cause is apparent. It is in this scenario that the risk of a haematological cancer with pallor, for example, is 0.43% (Table 5). Most parents would presumably wish their child to be tested if they were informed that the risk of a haematological cancer was of that magnitude, especially given the background incidence of 0.15 per 10 000 (0.0015% in a 3-month period).

Although 20% of patients diagnosed with central nervous system tumours consulted with vomiting in the 3 months prior to their diagnosis, the PPV suggests that only 4 in 10 000 children with vomiting will have a central nervous system tumour (compared to a background incidence of 0.08 per 10 000). GPs need to seek out other clues, including symptoms/signs of abnormal movement or visual disturbances, to refine the risk. This is similar to the scenario with adult brain tumours, where the risk from a new-onset adult headache reported to primary care is around 0.1%.[18] A previous study found 0.03% of children presenting with headache to primary care had an underlying brain tumour: the figures from the present study match that.[34] This is a classic opportunity for 'safety-netting', whereby GPs ensure that the child is

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Ethical approval

The conduct of this study was approved by the Independent Scientific Advisory Committee (ISAC) of the MHRA (Protocol 10_056) and the University of Bristol (reference: 35515).

Provenance

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Competing interests

The authors have declared no competing interests.

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followed up if the expected recovery does not take place.

This study identified 12 symptoms that increase the probability of a cancer diagnosis tenfold, and even more when children presented multiple times within 3 months. Although 1 in 1000 seems, and is, a small risk, it remains better than relying upon primary care clinicians to use intuition alone in making what will be a once-in-a-lifetime diagnosis.[35]

These symptoms and consultation patterns could be integrated into GP computer systems (as is currently being done for adult cancers), allowing a prompt to alert the GP to at least consider childhood cancer as a possibility when the appropriate combination occurs. Such prompts have an educational function too, and should reinforce knowledge of the relevant symptoms. Finally, the UK NICE guidance for recognition of suspected cancer is currently being updated; the symptoms reported here will improve the credibility of any new recommendations, as they are based on a primary care source.

REFERENCES

1. Cancer Research UK. Cancer Stats. *Childhood cancer — Great Britain and UK*. London: Cancer research UK, 2010. http://publications.cancerresearchuk.org/downloads/Product/CS_CS_CHILDHOOD.pdf (accessed 22 Nov 2012).
2. Craft AW, Pritchard-Jones K. UK childhood cancer survival falling behind rest of EU? *Lancet Oncol* 2007; **8(8):** 662–663.
3. Abdel-Rahman M, Stockton D, Rachet B, *et al*. What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable? *Br J Cancer* 2009; **101(suppl 2):** 115S–124S.
4. Department of Health. *Cancer Reform Strategy: achieving local implementation – second annual report*. London: DoH, 2007.
5. Department of Health. *Improving outcomes: a strategy for cancer*. London: DoH, 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_123394.pdf (accessed 22 Nov 2012).
6. Dixon-Woods M, Findlay M, Young B, *et al*. Parents' accounts of obtaining a diagnosis of childhood cancer. *Lancet* 2001; **357(9257):** 670–674.
7. Larsen MB, Hansen RP, Olesen F, Vedsted P. Patients' confidence in their GP before and after being diagnosed with cancer. *Br J Gen Pract* 2011; DOI: 10.3399/bjgp11X572409.
8. National Institute for Health and Clinical Excellence. *Referral guidelines for suspected cancer*. London: NICE, 2005 (updated 2011). http://www.nice.org.uk/nicemedia/live/10968/29814/29814.pdf (accessed 22 Nov 2012).
9. Dommett RM, Redaniel MT, Stevens MC, *et al*. Features of childhood cancer in primary care: a population-based nested case-control study. *Br J Cancer* 2012; **106(5):** 982–987.
10. Ahrensberg JM, Hansen RP, Olesen F, *et al*. Presenting symptoms of children with cancer: a primary-care population-based study. *Br J Gen Pract* 2012; DOI: 10.3399/bjgp12X652319.
11. *General Practice Research Database*. http://www.gprd.com/_docs/GPRD%20Practice%20Patient%20Populations%20Jul2011.pdf (accessed 22 Nov 2012).
12. Office for National Statistics. *Key health statistics from general practice 1998*. Series MB 6 No.2. London: ONS, 2000.
13. Herrett E, Thomas SL, Schoonen WM, *et al*. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; **69(1):** 4–14.
14. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010; **60(572):** e128–136.
15. Hamilton W, Lancashire R, Sharp D, *et al*. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. *Br J Cancer* 2008; **98(2):** 323–327.
16. Hamilton W, Lancashire R, Sharp D, *et al*. The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study. *BMC Med* 2009; **7:** 17.
17. Lawrenson R, Logie J, Marks C. Risk of colorectal cancer in general practice patients presenting with rectal bleeding, change in bowel habit or anaemia. *Eur J Cancer Care* 2006; **15(3):** 267–271.
18. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. *Br J Gen Pract* 2007; **57(542):** 695–699.
19. Jones R, Latinovic R, Charlton J, Gulliford MC. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. *BMJ* 2007; **334(7602):** 1040.
20. World Health Organization. *The International Classification of Diseases and Related Health Problems –tenth revision . Classification of Mental and Behavioural Disorders*. Geneva: WHO, 1992.
21. Adams ST, Leveson SH. Clinical prediction rules. *BMJ* 2012; **344:** d8312.
22. Hamilton W. The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients. *Br J Cancer* 2009; **101(suppl 2):** 80S–86S.
23. Knottnerus JA. *The evidence base of clinical diagnosis*. London: BMJ Books, 2002.
24. Office for National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 2007, England*. Series MB1 no.38. London: Office for National Statistics, 2009.
25. ISD Online. *Childhood, teenage and young adult cancers*. http://www.isdscotlandarchive.scot.nhs.uk/isd/1631.html (accessed 22 Nov 2012).
26. Welsh Cancer Intelligence and Surveillance Unit. *Cancer incidence in Wales, 2004–2008*. Cardiff: Welsh Cancer Intelligence and Surveillance Unit, 2010. http://www.wales.nhs.uk/sites3/Documents/242/incpub2010.pdf (accessed 22 Nov 2012).
27. Northern Ireland Cancer Registry. *Cancer incidence and mortality*. http://www.qub.ac.uk/research-centres/nicr/FileStore/PDF/Incidence/Filetoupload,210729,en.pdf (accessed 22 Nov 2012).
28. Stiller C, Kroll M, Eatock E. Incidence of Childhood Cancer 1991–2000. In: Stiller C (ed.). *Childhood cancer in Britain: incidence, survival, mortality*. Oxford: Oxford University Press, 2007; 23–106.
29. Thulesius H, Pola J, Hakansson A. Diagnostic delay in pediatric malignancies — a population-based study. *Acta Oncol* 2000; **39(7):** 873–876.
30. Wilne SH, Ferris RC, Nathwani A, Kennedy CR. The presenting features of brain tumours: a review of 200 cases. *Arch Dis Child* 2006; **91(6):** 502–506.
31. Wilne S, Collier J, Kennedy C, *et al*. Presentation of childhood CNS tumours: a systematic review and meta-analysis. *Lancet Oncol* 2007; **8(8):** 685–695.
32. Mag N, Abdullah W, Peng L, Lee C. Presenting features and treatment outcome of 78 malaysian children with neuroblastoma. *Southeast Asian J Trop Med Public Health* 1999; **30(1):** 149–153.
33. Widhe B, Widhe T. Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. *J Bone Joint Surg Am* 2000; **82(5):** 667–674.
34. Kernick D, Stapley S, Campbell J, Hamilton W. What happens to new onset headache in children that present to primary care? A case-cohort study using electronic primary care records. *Cephalalgia* 2009; *29(12):* 1311–1316.
35. Stolper E, van Bokhoven M, Houben P, *et al*. The diagnostic role of gut feelings in general practice A focus group study of the concept and its determinants. *BMC Fam Pract* 2009; **10(1):** 17.