Features of cancer in teenagers and young adults in primary care: a population-based nested case–control study

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Background: Teenagers and young adults (TYA, 15–24 years) diagnosed with cancer report repeated visits to primary care before referral. We investigated associations of symptoms and consultation frequency in primary care with TYA cancers.

Methods: Population-based, case–control study was carried out using data from the Clinical Practice Research Datalink (CPRD). A total of 1064 TYA diagnosed with cancer were matched to 13 206 controls. Symptoms independently associated with specific cancers were identified. Likelihood ratios (LRs) and positive predictive values (PPVs) were calculated.

Results: In the 3 months before diagnosis, 397 (42.9%) cases consulted $\geqslant 4$ times vs 593(11.5%) controls (odds ratio (OR): 12.1; 95% CI: 9.7, 15.1), yielding a PPV for any cancer of 0.018%. The LR of lymphoma with a head/neck mass was 434 (95% CI: 60, 3158), with a PPV of 0.5%. Corresponding figures in other cancers included – LR of leukaemia with lymphadenopathy (any site): 29 (95% CI: 8, 112), PPV 0.015%; LR of CNS tumour with seizure: 56 (95% CI: 19, 163), PPV 0.024%; and LR of sarcoma with lump/mass/swelling: 79 (95% CI: 24, 264), PPV 0.042%.

Conclusion: Teenagers and young adults with cancer consulted more frequently than controls in the 3 months before diagnosis. Primary care features of cancer match secondary care reports, but were of very low risk; nonetheless, some features increased the likelihood of cancer substantially and should be taken seriously when assessing TYA.

Teenagers and young adults (TYA, 15–24 years) with cancer frequently report repeated visits to primary care before referral for investigation (Smith *et al*, 2007). Improving early diagnosis is a priority for TYA (Smith *et al*, 2007), reflected in UK cancer policy (Department of Health, 2007, 2011). Delayed diagnosis reduces the confidence of patients and parents in their doctor (Dixon-Woods *et al*, 2001; Larsen *et al*, 2011), but its impact on survival in TYA is unknown.

Potential cancer diagnoses are diverse in this age group, early symptoms are often nonspecific, may be explained by more common illnesses and, because cancer in TYAs is rare (Birch *et al*, 2002), are low on the list of differential diagnoses for a general practitioner (GP). The aim of this study was to investigate the risk of cancer in TYA presenting to primary care with symptoms and/or increased consultation frequency.

METHODS

Study design. This was a population-based, case–control study nested within a cohort of TYA registered with the UK Clinical Practice Research Datalink (CPRD) (www.cprd.com). The CPRD is

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a prospectively gathered, anonymised database that holds long-itudinal administrative, clinical and prescribing records (including all consultations and diagnoses) of 11 million patients, from over 600 general practices across the UK (covering approximately 8% of the population; Clinical Practice Research Datalink, 2011). Data from the CPRD has been used in a number of studies to identify and quantify the symptoms of cancer (Hamilton *et al*, 2009; Shephard *et al*, 2012; Stapley *et al*, 2012; Dommett *et al*, 2012, 2013).

Study population. The sample comprised TYA aged 15–24 years, inclusive, drawn from all GP practices contributing to the CPRD since it was established on 1 January 1988 to 31 December 2010. Inclusion criteria and case–control definitions are as described previously (Dommett, 2013).

Symptoms and consultations. Consultations in the 12 months before diagnosis were identified. Libraries of codes representing individual features of possible cancer in TYA were assembled using established methodology (Dommett *et al*, 2012, 2013). Acne was considered to be unrelated to cancer and was included as a control condition to identify any recording bias (patients with cancer may attend more frequently, giving more opportunities for symptom recording).

Analysis. The magnitudes of associations of symptoms and patterns of consultation frequency with cancer were identified using univariable conditional logistic regression. Only variables occurring in $\geqslant 2\%$ of either cases or controls, and with a univariable *P*-value $\leqslant 0.1$ entered the multivariable analyses (Hamilton, 2009). We used a 'conservative' *P*-value of < 0.01 for retention in the final model, to avoid false-positive associations arising from multiple testing. Positive predictive values (PPV) were calculated as described previously (Dommett, 2013).

Sample sizes were predetermined by the total number of cancers in the CPRD, so we performed a power calculation, using a two-sided 5% significance. A study with 300 cases (e.g., lymphoma) each 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 (e.g., bone), 80 cases had 84% power to identify a similar change and 97% power for a change in a commoner variable from 30% in controls to 50% in cases.

RESULTS

In all, 1064 eligible cases and 13 206 eligible controls were identified. Their cancer diagnoses are summarised in Supplementary Table 1 online.

Consultation frequency. In the 12 months before diagnosis, cases had a median of five consultations (interquartile range (IQR): 3–9) compared with two (IQR: 0–4) in controls ($P < 0.001$). Among cases, 95.2% had consulted in the year before diagnosis compared with 71.1% of controls (odds ratio (OR) 9.0; 95% CI: 6.8–12.1) (Supplementary Table 2 online). Differences in consultation rates were most apparent in the 3 months immediately before diagnosis, cases having a median of three consultations (IQR 1–5) compared with no consultations (IQR 0–1) in controls ($P < 0.001$). This difference was consistent across all diagnostic groups in both cases and controls (Supplementary Figure 1 online).

Among cases, 86.9% had seen their GP in the 3 months before cancer diagnosis compared with 38.8% of controls (OR: 12.4; 95% CI: 10.3–15.0) (Table 1). Of these, 42.9% of cases had consulted four times or more compared with 11.5% of controls (OR: 12.1; 95% CI: 9.7–15.1). However, the PPV for cancer in a TYA patient consulting four times or more in 3 months was only 0.018%; that is, of 10 000 TYA consulting four times or more in 3 months, only around two would be diagnosed with cancer (based on a prior probability of cancer of 0.49 in 10 000 in 3 months) (Birch *et al*, 2002).

Identification of independent associations with cancer. Because of the diversity of diagnoses in our cohort, symptom analysis was limited to four predefined disease groups: leukaemia (annual incidence: 0.21 per 10 000); lymphoma (annual incidence: 0.47 per 10 000); CNS tumours (annual incidence: 0.17 per 10 000); and bone/soft tissue sarcoma (annual incidence: 0.21 per 10 000) (Birch *et al*, 2002). The multivariable models for each group are shown in Table 2.

Four features remained in the final model for leukaemia, of which lympadenopathy had the highest PPV of 1.5 per 10 000 (95% CI: 0.4–5.78).

Four features remained in the final model for lymphoma, of which lump/mass/swelling of the head and neck had the highest PPV of 50.34 per 10 000 (95% CI: 6.96–367.86). The second highest PPV was for lymphadenopathy followed by lump/mass/swelling

Table 1. The association between the number of consultations[a] and a diagnosis of cancer

Number of consultations	Case N = 1064		Control N = 13 206		OR[b]	Likelihood ratio	Positive predictive value (per 10 000) (95% CI)
	Freq.	%[c]	Freq.	%[c]			
0–3 months before index date							
No consultatios	139	13.06	8071	61.12	1.0		
With consultations	925	86.94	5135	38.88	12.4 (10.3–15.0)	2.24	1.1 (1.07–1.14)
1	195	21.08	2860	55.70	1.0		
2	190	20.54	1150	22.40	2.6 (2.1–3.2)	0.92	0.45 (0.39–0.52)
3	143	15.46	532	10.36	4.5 (3.5–5.8)	1.49	0.73 (0.62–0.87)
4 or more	397	42.92	593	11.55	12.1 (9.7–15.1)	3.72	1.83 (1.65–2.04)

Abbreviations: CI = confidence interval; Freq. = frequency; GP = general practitioner; OR = odds ratio.
[a]All primary care consultations including out of hours and telephone consultations.
[b]Represents the odds of being diagnosed with cancer given more consultations with the GP; computed using conditional logistic regression.
[c]For categories 1, 2, 3 and 4 or more, proportions reflect only patients with consultations.

Table 2. Multivariable analysis of the features of specific TYA cancers: (A) leukaemia, (B) lymphoma, (C) CNS tumours and (D) bone tumour/soft tissue sarcoma

(A) Leukaemia

Symptom[a]	Cases (N = 143)		Control (N = 1799)		OR	95% Confidence interval	P-value	LR	95% Confidence interval	PPV (per 10 000)	95% Confidence interval
	Freq.	%	Freq.	%							
Lymphadenopathy[b]	7	4.90	3	0.17	7.65	1.55–37.72	0.0124	29.35	7.67–112.30	1.51	0.40–5.78
Fatigue	15	10.49	8	0.44	12.69	4.48–35.96	<0.0001	23.59	10.17–54.69	1.21	0.52–2.82
Bruising	9	6.29	5	0.28	24.72	4.71–129.78	<0.0002	22.64	7.69–66.67	1.17	0.40–3.43
Three or more consultations	74	51.75	125	6.95	5.92	3.71–9.44	<0.0001	7.45	5.91–9.39	0.38	0.30–0.48

(B) Lymphoma

Symptom[a]	Cases (N = 270)		Control (N = 3350)		OR	95% Confidence interval	P-value	LR	95% Confidence interval	PPV (per 10 000)	95% Confidence interval
	Freq.	%	Freq.	%							
Lump mass swelling head and neck	35	12.96	1	0.03	71.85	8.98–575.07	0.0001	434.26	59.72–3157.62	50.34	6.96–367.86
Lymphadenopathy	77	28.52	4	0.12	184.46	40.65–837.06	<0.0001	238.84	88.09–647.59	27.75	10.26–75.44
Lump mass swelling[c]	29	10.74	15	0.45	14.08	5.33–37.19	<0.0001	23.99	13.02–44.19	2.79	1.52–5.15
Three or more consultations	175	64.81	294	8.78	7.67	4.92–11.95	<0.0001	7.39	6.42–8.50	0.86	0.75–0.99

(C) CNS tumours

Symptom[a]	Cases (N = 154)		Control (N = 1906)		OR	95% Confidence interval	P-value	LR	95% Confidence interval	PPV (per 10 000)	95% Confidence interval
	Freq.	%	Freq.	%							
Seizure	18	11.69	4	0.21	17.5	5.12–59.83	<0.0001	55.69	19.09–162.52	2.38	0.82–6.95
Headache	33	21.43	12	0.63	18.91	7.11–50.25	<0.0001	34.04	17.95–64.55	1.45	0.77–2.76
Vomiting	11	7.14	5	0.26	7.31	1.65–32.47	0.0089	27.23	9.58–77.37	1.16	0.41–3.31
Pain	11	7.14	20	1.05	6.11	2.25–16.57	0.0004	6.81	3.32–13.95	0.29	0.14–0.6
Three or more consultations	73	47.4	165	8.66	3.04	1.82–5.09	<0.0001	5.48	4.39–6.83	0.23	0.19–0.29

(D) Bone tumours/soft tissue sarcoma

Symptom[a]	Cases (N = 196)		Control (N = 2438)		OR	95% Confidence interval	P-value	LR	95% Confidence interval	PPV (per 10 000)	95% Confidence interval
	Freq.	%	Freq.	%							
Lump mass swelling	19	9.69	3	0.12	39.62	8.17–192.1	<0.0001	78.78	23.52–263.91	4.15	1.24–13.92
Musculoskeletal symptoms	37	18.88	26	1.07	8.37	4.18–16.76	<0.0002	17.7	10.95–28.61	0.93	0.58–1.51
Three or more consultations	86	43.88	189	7.75	3.88	2.48–6.06	<0.0003	5.66	4.59–6.98	0.3	0.24–0.37
Chest pain[b]	5	2.55	12	0.49	5.15	1.47–17.99	0.0103	5.18	1.84–14.56	0.27	0.1–0.77

Abbreviations: CNS = central nervous system; Freq. = frequency; LR = likelihood ratio; OR = odds ratio; PPV = positive predictive value; TYA = teenagers and young adults.
[a]Symptoms are ordered by PPV.
[b]Has a P-value below the threshold, but is needed in the model based on the LR test.
[c]Lump mass swelling below neck not including abdomen.

below neck excluding abdomen, and it is presumed that all three of these features are likely to represent lymphadenopathy. When lump/mass/swelling of the head and neck, lymphadenopathy and lump/mass/swelling below neck excluding abdomen are combined as a single symptom the PPV is 9.03 per 10 000 (95% CI: 5.73–14.25).

The CNS tumour model contained five features, with seizure having the highest PPV of 2.38 per 10 000 (95% CI: 0.82–6.95). In this group, 8.4% of cases had visual symptoms, but a PPV could not be calculated as no controls had this feature.

Four variables were independently associated with bone/soft tissue sarcomas, with lump/mass/swelling below neck, excluding abdomen, having the highest PPV of 4.15 per 10 000 (95% CI: 1.24–13.92).

The OR and LR for our control condition, acne, were 1.32 (95% CI: 0.8–2.19) and 1.31 (95% CI: 0.8–2.14), respectively, indicating little evidence of recording bias.

DISCUSSION

This is the first study of TYA cancer to use prospectively collected primary care data. The distribution of cancers was largely representative of the diagnoses seen in TYA, with lymphoma the most common diagnosis overall (25.4%). We chose to study symptoms and consultations in the 3 months before a diagnosis. This was a practical compromise, being a period over which it is clinically reasonable for a GP to monitor symptoms.

Teenagers and young adults with cancer see their doctors more frequently than controls, particularly in the 3 months before diagnosis. Even so, because TYA cancer is rare, the absolute risk of cancer in a patient consulting four or more times is only 1.8 per 10 000. The consultation rates observed are consistent with retrospective case note analyses (Fern, et al, 2011) and patient reports (Lyratzopoulos et al, 2012; Smith et al, 2007). The high percentage of patients with multiple consultations may represent the complexity of a cancer diagnosis in this age group and supports advice advocating referral if a patient attends several times with the same problem, without a clear diagnosis (National Institute for Health and Clinical Excellence, 2005).

The use of electronic primary care records has limitations as it is well recognised that GPs preferentially record diagnoses as opposed to unexplained symptoms. Under-recording should not affect likelihood ratios (which underpin PPVs) as long as it is consistent between cases and controls, but may lead to an overestimation of PPVs, and they will only remain valid if GP recording and patient consultation behaviour do not change with time (Hamilton, 2012; Shapley et al, 2010).

Our findings confirm the clinical significance of the commonly perceived symptoms of cancer in this age group, as expected symptom patterns emerged for the different diagnostic groups closely matching reports from secondary care. Absolute risks of specific cancers with symptoms have not been estimated previously, although we expected them to be small. Yet, despite the small absolute risks, some features substantially altered the prior probability of a subsequent diagnosis of cancer. The presence of a lump, mass or swelling of the head and neck increased the prior probability of lymphoma from 0.12 per 10 000 in any 3-month period to a posterior probability of 50.3 per 10 000, a more than 400-fold increase in probability. Of note, visual symptoms were not recorded in controls, but were frequent in CNS tumours, implying that investigation is clearly appropriate.

As TYA cancer diagnosis is rare, PPVs will never be particularly high; thus, the question for primary care remains: should a raised relative risk trigger investigation, even when the absolute risk is very small? We believe the seriousness of TYA cancer, coupled with the high potential for cure, justifies investigation at a lower level of probability than might be considered appropriate for later onset adult cancers. Safety-netting procedures are particularly appropriate where, for example, non-resolving musculoskeletal symptoms follow a minor sports injury, may be indicative of a bone/soft tissue sarcoma. This may be especially relevant in this age group as TYAs evolve towards independent health-care-seeking behaviour.

CONCLUSION

The perception of delay in diagnosis in TYA can have major implications on their subsequent cancer journey. The symptoms identified for common cancers in this age group are not unexpected, but some substantially alter the prior probability of a cancer diagnosis. NICE guidance for recognition of suspected cancer is currently being updated in the United Kingdom and the symptoms reported here should enhance the credibility of new recommendations, as they derive from primary care data. Further studies of TYA consultation behaviour and of how symptoms are interpreted both by the GP and the patient are required to fully understand their impact on time to diagnosis, and on how this can be minimised.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The interpretation and conclusions contained in this study are those of the author/s alone.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)