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Cancer

Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases

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Abstract

Background: High birthweight is an established risk factor for childhood leukaemia. Its association with other childhood cancers is less clear, with studies hampered by low case numbers.

Methods: We used two large independent datasets to explore risk associations between birthweight and all subtypes of childhood cancer. Data for 16 554 cases and 53 716 controls were obtained by linkage of birth to cancer registration records across five US states, and 23 772 cases and 33 206 controls were obtained from the UK National Registry of Childhood Tumours. US, but not UK, data were adjusted for gestational age, birth order, plurality, and maternal age and race/ethnicity.

Results: Risk associations were found between birthweight and several childhood cancers, with strikingly similar results between datasets. Total cancer risk increased linearly with each 0.5 kg increase in birthweight in both the US [odds ratio 1.06 (95% confidence interval 1.04, 1.08)] and UK [1.06 (1.05, 1.08)] datasets. Risk was strongest for leukaemia [USA: 1.10 (1.06, 1.13), UK: 1.07 (1.04, 1.10)], tumours of the central nervous system [USA: 1.05 (1.01, 1.08), UK: 1.07 (1.04, 1.10)], renal tumours [USA: 1.17 (1.10, 1.24), UK: 1.12 (1.06, 1.19)] and soft tissue sarcomas [USA: 1.12 (1.05, 1.20), UK: 1.07 (1.00, 1.13)]. In contrast, increasing birthweight decreased the risk of hepatic tumours [USA: 0.77 (0.69,

0.85), UK: 0.79 (0.71, 0.89) per 0.5 kg increase]. Associations were also observed between high birthweight and risk of neuroblastoma, lymphomas, germ cell tumours and malignant melanomas. For some cancer subtypes, risk associations with birthweight were non-linear. We observed no association between birthweight and risk of retinoblastoma or bone tumours.

Conclusions: Approximately half of all childhood cancers exhibit associations with birthweight. The apparent independence from other factors indicates the importance of intrauterine growth regulation in the aetiology of these diseases.

Key words: Birthweight, intrauterine growth, childhood cancer, case-control study

Key Messages

- Birthweight is associated with risk of approximately half of all childhood cancers.
- Increasing birthweight raises the risk of leukaemia, tumours of the central nervous system, renal tumours, soft tissue sarcomas, neuroblastoma, lymphoma, germ cell tumours and other malignant neoplasms/melanomas.
- Decreasing birthweight raises the risk of hepatic tumours.
- Some cancer subtypes (hepatoblastoma, Wilms tumour, intracranial and intraspinal germ cell tumours and acute myeloid leukaemia) associate with birthweight in a non-linear manner.
- Risks of retinoblastomas and bone tumours do not appear to associate with birthweight.
- Birthweight associates with risk of childhood cancers independently of gestational age, birth order, plurality, maternal age and maternal race/ethnicity.
- Further studies are needed to understand the biological mechanisms linking birthweight with risks of childhood cancer.

Introduction

The causes of childhood cancer are largely unknown. The early age at onset of many childhood cancers,[1] and presence of premalignant leukaemia clones at birth,[2] suggest that prenatal influences play a role in their aetiologies.

High birthweight is associated with risk of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in childhood.[3,4] It has been proposed that higher levels of circulating growth factors in pregnancies leading to big babies may have oncogenic effects on the developing immune system, increasing the risk of progression to leukaemia.[5,6] Risk of central nervous system (CNS) tumours,[7] neuroblastoma[8] and Wilms tumour[9] may also be linked to birthweight, suggesting an underlying and potentially key relationship between *in utero* tissue growth/development and cancer risk. However, low case numbers have been a limitation of these studies, and controversy remains. Little is known about the risk relationship between birthweight and other childhood tumours.

Here we have used two large, independent population-based datasets to analyse the relationship between birthweight and the entire spectrum of childhood tumours.

Methods

US data collection

Data were pooled from case-control studies conducted in California, Minnesota, New York, Texas and Washington.[10] Cases were identified from population-based cancer registries, and controls were randomly selected from birth records, with ratios ranging from 1:1 to 10:1. Frequency matching was used for all states apart from California, where individual matching was employed. All states matched by year of birth; California and Texas also matched by sex. Cases diagnosed and controls dying neonatally were excluded, as were most with Down syndrome (DS) recorded on their birth certificates (not recorded in Texas or Washington before 1984 and 1989, respectively). The remaining 17 672 cases and 57 966 frequency-matched controls are summarized in Table 1.

Birthweight, gestational age, plurality, gender, birth order, year of birth, and maternal age and race were obtained from birth records. Only subjects with values for each of these were included in the analysis. Gestational ages calculated from last menstrual period (LMP) and clinical date estimates were provided by four states (California only the LMP). Gestational age calculation prioritized the

Table 1. Description of datasets available from each state participating in the US pooled analysis and the UK analysis

Dataset	Age at diagnosis	Diagnosis period	Years of birth	Cases (% dataset)	Controls (% dataset)	Matching factors
USA[a]						
California	28 d-4 y	1988–1997	1983–1997	4177 (24%)	8730 (15%)	Birth year, sex
Minnesota	28 d-14 y	1988–2004	1976–2004	2170 (12%)	8735 (15%)	Birth year
New York	28 d-14 y	1985–2001	1970–2001	4357 (25%)	12 041 (21%)	Birth year
Texas	28 d-14 y	1990–1998	1975–1998	4647 (26%)	4732 (8%)	Birth year, sex
Washington	28 d-14 y	1980–2004	1980–2004	2321 (13%)	23 728 (41%)	Birth year
TOTAL				17 672 (100%)	57 966 (100%)	
UK[b]						
England and Wales	0–14 y	1980–2007	1980–2007	25 649 (100%)	34 082 (100%)	Birth period, sex, birth registration sub-district

d, days; y, years.
[a]US data were obtained by linkage of birth registration to cancer registration.
[b]UK data were obtained from the National Registry of Childhood Tumours.

LMP estimate when available.[10] All subjects with plausible birthweights and gestational ages[11,12] were included in the analysis, but birthweights recorded as <0.5 or ≥6.0 kg and gestational ages recorded as <20 or >45 weeks were considered inaccurate and treated as missing. Also excluded were birthweights for gestational age suggested to be unreliable by expert guidelines.[10] 16 554 cases and 53 716 controls remained after exclusions.

UK data collection

The UK National Registry of Childhood Tumours (NRCT) includes all malignancies and brain tumours diagnosed in children aged 0–14 years while domiciled in England, Wales and Scotland from 1962 (and in Northern Ireland from 1993) to 2010.[13] Birth registration information for most NRCT cases was routinely obtained from the Office for National Statistics and the General Registry Office Scotland. One (or two since 2000) control birth records were also routinely selected, individually matched on sex, district and sub-district of registration and being born within 6 months of the case. No controls were diagnosed with childhood cancer at time of selection. Birthweight was available for 95% of England and Wales NRCT cases and controls born and diagnosed 1980–2007 (25 649 cases, 34 082 controls, Table 1). Birth registration records available to the NRCT do not routinely document DS, so these children were not excluded from the study. As for US data, birthweights recorded as <0.5 kg and ≥6.0 kg were excluded. The informative sets included 23 772 cases and 33 206 controls.

Statistical analysis

The International Classification of Childhood Cancers third edition was used to classify tumour subtypes (Tables 2–6, Figure 1, and Supplementary Tables S1–S3 available at *IJE* online).

US data were analysed using unconditional logistic regression in SAS 9.2 with odds ratios (ORs) adjusted for gender, state and year of delivery. Further adjustment was made for gestational age. Maternal age, plurality, birth order and maternal race/ethnicity were also included in the analysis since they are established/suspected risk factors for several childhood cancers,[14–17] with known association to birthweight.[18] ORs and 95% confidence intervals (CIs) were calculated considering birthweight as a continuous variable (trend per 0.5 kg increase in birthweight) as well as a categorical variable (with 3.00–3.49 kg as the reference).

UK data were analysed using STATA 11, using conditional logistic regression based on the individually matched case-control sets. Birth registration records from England and Wales do not routinely document gestation, maternal age, plurality, birth order or maternal race/ethnicity, so we were unable to adjust for these potential confounders for this dataset. ORs and 95% CIs were calculated considering birthweight as a continuous and a categorical variable, as for the US data.

Fractional polynomial approaches examined all cancer subtypes with at least 100 cases, using R for US data and STATA 11 for UK data. These methods allowed us to test transformations using powers in the set (−2, −1, −0.5, 0, 0.5, 1, 2, 3) to determine the best-fitting model, including up to two terms in each. Tests of difference in deviance determine whether the fit is significantly worse than a one-term model. If complex models performed no better, the linear term was maintained. All US models included terms for state, birth year and sex as matching variables. Modelling UK data necessarily included the control matching variables.

Table 2. Infant and disease characteristics of the study populations

Cancer	Dataset[a]	Sex, no. (%)		Gestational age, mean (SD), weeks	Age at diagnosis, mean (SD), years	Birthweight category, no. (%), kg						Birthweight, mean (SD), kg
		Male	Female			0.50–1.99	2.00–2.49	2.50–2.99	3.00–3.49	3.50–3.99	≥4.00	
Controls	USA	28 336 (52.8)	25 380 (47.2)	39.53 (2.39)		945 (1.8)	1957 (3.6)	7537 (14.0)	19 493 (36.3)	16 959 (31.6)	6825 (12.7)	3.41 (0.57)
	UK	18 176 (54.7)	15 030 (45.3)			736 (2.2)	1385 (4.2)	5543 (16.7)	12 296 (37.0)	9616 (29.0)	3630 (10.9)	3.34 (0.58)
Total cancers	USA	9123 (55.1)	7431 (44.9)	39.39 (2.46)	5.02 (4.10)	332 (2.0)	608 (3.7)	2274 (13.7)	5726 (34.6)	5358 (32.4)	2256 (13.6)	3.42 (0.59)
	UK	13 023 (54.8)	10 749 (45.2)		5.03 (4.18)	447 (1.9)	948 (4.0)	3696 (15.6)	8558 (36.0)	7237 (30.4)	2886 (12.1)	3.38 (0.57)
Leukaemias	USA	3124 (56.2)	2437 (43.8)	39.43 (2.33)	4.60 (3.45)	82 (1.5)	185 (3.3)	716 (12.9)	1956 (35.2)	1837 (33.0)	785 (14.1)	3.45 (0.56)
	UK	4334 (55.4)	3492 (44.6)		4.54 (3.63)	135 (1.7)	319 (4.1)	1226 (15.7)	2786 (35.6)	2385 (30.4)	1175 (10.9)	3.39 (0.57)
CNS tumours	USA	1977 (55.5)	1584 (44.5)	39.56 (2.33)	5.58 (4.02)	63 (1.8)	137 (3.8)	484 (13.6)	1248 (35.0)	1142 (32.1)	487 (13.7)	3.42 (0.58)
	UK	3085 (54.1)	2617 (45.9)		5.70 (4.08)	94 (1.7)	220 (3.9)	895 (15.7)	2074 (36.4)	1750 (30.7)	669 (11.7)	3.38 (0.56)
Lymphomas	USA	885 (63.4)	511 (36.6)	39.40 (2.41)	8.02 (4.42)	23 (1.6)	54 (3.9)	208 (14.9)	485 (34.7)	438 (31.4)	188 (13.5)	3.41 (0.57)
	UK	1373 (68.0)	647 (32.0)		8.34 (3.95)	26 (1.3)	69 (3.4)	311 (15.4)	732 (36.2)	618 (30.6)	264 (13.1)	3.40 (0.55)
Soft tissue sarcomas	USA	552 (55.2)	448 (44.8)	39.45 (2.33)	5.76 (4.36)	15 (1.5)	31 (3.1)	147 (14.7)	315 (31.5)	356 (35.6)	136 (13.6)	3.45 (0.56)
	UK	868 (56.3)	673 (43.7)		5.30 (4.32)	28 (1.8)	72 (4.7)	229 (14.9)	567 (36.8)	471 (30.6)	174 (11.3)	3.37 (0.56)
Neuroblastoma	USA	789 (54.7)	654 (45.3)	39.28 (2.45)	2.22 (2.32)	37 (2.6)	60 (4.2)	212 (14.7)	475 (32.9)	466 (32.3)	193 (13.4)	3.40 (0.61)
	UK	967 (53.6)	836 (46.4)		1.93 (2.30)	44 (2.4)	74 (4.1)	296 (16.4)	640 (35.5)	543 (30.1)	206 (11.4)	3.34 (0.57)
Renal tumours	USA	543 (47.2)	608 (52.8)	39.28 (2.42)	3.15 (2.35)	20 (1.7)	40 (3.5)	171 (14.9)	375 (32.6)	368 (32.0)	177 (15.4)	3.45 (0.61)
	UK	736 (47.6)	810 (52.4)		2.79 (2.50)	30 (1.9)	58 (3.8)	223 (14.4)	546 (35.3)	476 (30.8)	213 (13.8)	3.41 (0.61)
Bone tumours	USA	262 (51.3)	249 (48.7)	39.37 (2.37)	9.83 (3.70)	7 (1.4)	26 (5.1)	70 (13.7)	189 (37.0)	161 (31.5)	58 (11.4)	3.39 (0.56)
	UK	378 (52.5)	342 (47.5)		9.80 (3.28)	12 (1.7)	22 (3.1)	110 (15.3)	279 (38.8)	221 (30.7)	76 (10.6)	3.38 (0.55)
Germ cell tumours	USA	279 (52.9)	248 (47.1)	39.36 (2.55)	5.44 (5.23)	7 (1.3)	20 (3.8)	75 (14.2)	183 (34.7)	171 (32.4)	71 (13.5)	3.42 (0.58)
	UK	380 (48.4)	405 (51.6)		4.94 (5.10)	25 (3.2)	24 (3.1)	136 (17.3)	275 (35.0)	228 (29.0)	97 (12.4)	3.35 (0.62)
Other carcinomas and melanomas	USA	162 (44.3)	204 (55.7)	39.27 (2.52)	9.98 (4.18)	9 (2.5)	16 (4.4)	54 (14.8)	130 (35.5)	118 (32.2)	39 (10.7)	3.37 (0.59)
	UK	248 (44.1)	315 (56.0)		9.33 (4.11)	8 (1.4)	29 (5.2)	73 (13.0)	191 (33.9)	190 (33.8)	72 (12.8)	3.42 (0.59)
Retinoblastoma	USA	332 (50.3)	328 (49.7)	39.28 (2.62)	1.76 (1.62)	19 (2.9)	24 (3.6)	94 (14.2)	259 (39.2)	192 (29.1)	72 (10.9)	3.36 (0.60)
	UK	425 (50.7)	414 (49.3)		1.21 (1.60)	15 (1.8)	37 (4.4)	135 (16.1)	323 (38.5)	235 (28.0)	94 (11.2)	3.35 (0.56)
Hepatic tumours	USA	182 (60.5)	119 (39.5)	37.82 (4.76)	2.31 (2.88)	48 (15.9)	14 (4.7)	33 (11.0)	90 (29.9)	81 (26.9)	35 (11.6)	3.04 (1.03)
	UK	160 (58.2)	115 (41.8)		2.44 (3.48)	24 (8.7)	18 (6.6)	43 (15.6)	92 (33.5)	68 (24.7)	30 (10.9)	3.15 (0.84)
Other	USA	36 (46.8)	41 (53.2)	39.39 (3.22)	5.30 (4.74)	2 (2.6)	1 (1.3)	10 (13.0)	21 (27.3)	28 (36.4)	15 (19.5)	3.48 (0.62)
	UK	69 (45.4)	83 (54.6)		5.09 (4.63)	6 (4.0)	6 (4.0)	19 (12.5)	53 (34.9)	52 (34.2)	16 (10.5)	3.35 (0.63)

SD, standard deviation.

[a]Birthweights recorded as <0.5 kg or ≥6.0 kg were excluded. For the USA, gestational ages recorded as <20 weeks or >45 weeks were also excluded, as were participants with Down syndrome (this information was not available for the UK.)

Table 3. Childhood cancers whose risk associates with birthweight in both USA and UK datasets

Cancer	Dataset[a]	Cases	Controls	Trend per 0.5 kg increase in birthweight[b]
Total childhood cancer	USA	16 554	53 716	**1.06 (1.04–1.08)**
	UK	23 772	33 206	**1.06 (1.05–1.08)**
Leukaemias, myeloproliferative and myelodysplastic diseases				
Total	USA	5561	53 716	**1.10 (1.06–1.13)**
	UK	7826	10 785	**1.07 (1.04–1.10)**
Diagnosed <age 1 year	USA	386	53 716	1.09 (0.98–1.20)
	UK	593	788	1.00 (0.92–1.10)
Diagnosed at age 1–14 years	USA	5175	53 716	**1.10 (1.06–1.13)**
	UK	7233	9997	**1.08 (1.05–1.11)**
Lymphoid leukaemias	USA	4476	53 716	**1.11 (1.07–1.14)**
	UK	6284	8683	**1.08 (1.05–1.12)**
Acute myeloid leukaemias	USA	804	53 716	1.03 (0.96–1.11)
	UK	1144	1579	1.04 (0.98–1.12)
Chronic myeloproliferative diseases	USA	101	53 716	1.16 (0.95–1.40)
	UK	123	169	1.05 (0.86–1.28)
Myelodysplastic syndrome and other myeloproliferative diseases	USA	22	53 716	1.27 (0.86–1.88)
	UK	187	240	1.10 (0.94–1.30)
Unspecified and other specified leukaemias	USA	158	53 716	1.04 (0.89–1.21)
	UK	88	114	0.83 (0.66–1.04)
CNS and miscellaneous intracranial and intraspinal neoplasms				
Total	USA	3561	53 716	**1.05 (1.01–1.08)**
	UK	5702	8106	**1.07 (1.04–1.10)**
Ependymomas and choroid plexus tumour	USA	370	53 716	1.08 (0.97–1.20)
	UK	625	886	1.05 (0.96–1.16)
Astrocytomas	USA	1559	53 716	**1.06 (1.01–1.11)**
	UK	2368	3357	**1.09 (1.04–1.14)**
Intracranial and intraspinal embryonal tumours	USA	858	53 716	1.05 (0.98–1.13)
	USA[c]	894	57 569	**1.07 (1.01–1.14)**
	UK	1150	1593	**1.09 (1.02–1.17)**
Other gliomas	USA	467	53 716	0.99 (0.90–1.08)
	UK	609	864	1.00 (0.92–1.10)
Other specified intracranial and intraspinal neoplasms	USA	194	53 716	0.98 (0.84–1.13)
	UK	618	918	**1.11 (1.01–1.21)**
Unspecified intracranial	USA	113	53 716	1.09 (0.90–1.31)
	UK	332	488	0.93 (0.82–1.05)
Renal tumours				
Total	USA	1151	53 716	**1.17 (1.10–1.24)**
	UK	1546	2123	**1.12 (1.06–1.19)**
Wilms tumour and other nonepithelial renal tumours	USA	1129	53 716	**1.17 (1.10–1.24)**
	UK	1515	2072	**1.12 (1.05–1.18)**
Renal carcinomas	USA	16	53 716	1.38 (0.87–2.17)
	UK	16	24	1.69 (0.82–3.47)
Unspecified malignant renal tumours	USA	6	53 716	1.68 (0.83–3.38)
	UK	15	27	1.59 (0.72–3.54)
Soft tissue and other extraosseous sarcomas				
Total	USA	1000	53 716	**1.12 (1.05–1.20)**
	UK	1541	2081	**1.07 (1.00–1.13)**
Rhabdomyosarcomas[d]	USA	556	53 716	**1.17 (1.07–1.27)**
	UK	878	1159	1.06 (0.98–1.15)
Embryonal	USA	347	53 716	**1.25 (1.13–1.39)**
	UK	558	708	**1.12 (1.01–1.24)**
Alveolar	USA	81	53 716	0.88 (0.70–1.09)
	UK	201	298	1.02 (0.86–1.20)
NOS	USA	128	53 716	1.12 (0.94–1.33)
	UK	119	153	0.91 (0.73–1.13)

(Continued)

Table 3. Continued

Cancer	Dataset[a]	Cases	Controls	Trend per 0.5 kg increase in birthweight[b]
Fibrosarcomas, peripheral nerve sheath tumours	USA	120	53 716	1.03 (0.87–1.24)
and other fibrous neoplasms	UK	122	160	0.92 (0.74–1.13)
Other specified soft tissue sarcomas	USA	246	53 716	1.07 (0.94–1.21)
	UK	450	641	1.09 (0.97–1.21)
Unspecified soft tissue sarcomas	USA	76	53 716	1.12 (0.89–1.40)
	UK	91	121	1.24 (0.97–1.60)
Hepatic tumours				
Total	USA	301	53 716	***0.77 (0.69–0.85)***
	UK	275	397	***0.79 (0.71–0.89)***
Hepatoblastoma	USA	261	53 716	***0.73 (0.65–0.82)***
	UK	234	334	***0.81 (0.71–0.91)***
Hepatic carcinomas	USA	38	53 716	0.76 (0.56–1.04)
	UK	37	55	0.72 (0.49–1.06)
Unspecified malignant hepatic tumours	USA	2	53 716	n/d
	UK	4	8	0.48 (0.14–1.63)

n/d = not determined as only 2 cases.

[a]Data were adjusted for sex, period and region of birth. US data were further adjusted for gestational age, birth order, plurality, maternal age and race/ethnicity. This information was not available for UK data.

[b]Odds ratios (95% confidence intervals), considering birthweight as a continuous variable. Odds ratios whose 95% confidence intervals are above the null value (1) are bold, below the null value are bold italic. .

[c]Data unadjusted except for matching variables (state, year of birth and sex).

[d]Rhabdomyosarcomas: Embryonal typeicdo3 89 023, 89 103, 89 123, 89 913; Alveolar typeicdo3 89 203; NOS typeicdo3 89 003, 89 013.

Results

As expected, across the entire study population most cancer types were more prevalent in males, particularly the lymphomas and hepatic tumours (Table 2). Renal tumours and carcinomas/melanomas occurred more frequently among females, whereas retinoblastomas were distributed equally between the sexes. These distribution patterns were similar between US and UK datasets for all but the germ cell tumours, which displayed a contrasting male and female dominance in the USA and the UK, respectively. Mean age at diagnosis was comparable between datasets for each cancer, as was the proportion of individuals in each birthweight category. Mean birthweights were slightly greater for US compared with UK babies (3.41 kg vs 3.34 kg for controls, 3.42 kg vs 3.38 kg for total cancer cases). This pattern persisted for most cancer types, although the reverse was seen for carcinomas/melanomas and hepatic tumours, and there was negligible difference between datasets for the lymphomas, bone tumours and retinoblastomas.

US and UK datasets were analysed independently to determine risk associations between birthweight and risk of childhood cancer. Analysis of US data included adjustment for gestational age, maternal age, plurality, birth order and maternal race/ethnicity. This was not possible for the UK analysis, since information on these variables was not available.

Childhood cancers that associate with birthweight in both datasets

In both datasets, increasing birthweight associated with an increased risk of total childhood cancer, with each 0.5 kg increase in birthweight elevating risk by 6% (Table 3). Risk associations were observed for several tumour subgroups. For most there was a striking correlation between datasets, even though only US data were adjusted for potential confounders (Table 3).

Increasing birthweight associated with risk of leukaemias, CNS tumours, renal tumours and soft tissue sarcomas, but risk appeared specific to subsets of each. Leukaemia risk was strongest for the lymphoid leukaemias (USA: OR 1.11, UK: 1.08 per 0.5 kg increase in birthweight) and for children diagnosed age 1–14 years (USA: 1.10, UK: 1.08 per 0.5 kg increase). For CNS tumours, risk was most notable for astrocytomas (USA: 1.06, UK: 1.09 per 0.5 kg increase), although risk of intracranial and intraspinal embryonal tumours was also strong in the UK (1.09 per 0.5 kg increase). To understand the weaker association between this tumour type and birthweight in the USA, we investigated whether the calculated risk was influenced by confounder adjustment. Without adjustment for gestational age, maternal age, plurality, birth order and maternal race/ethnicity in the US analysis, the risk association strengthened (1.07 per 0.5 kg increase, Table 3), suggesting an influence of one or more of these variables in this

Table 4. Risk associations between birthweight and neuroblastoma

Cancer	Dataset[a]	Cases	Controls	Odds ratios (95% confidence intervals)[b]						
				Birthweight category (kg)						Trend per 0.5 kg increase in birthweight[c]
				0.50–1.99	2.00–2.49	2.50–2.99	3.00–3.49	3.50–3.99	≥4.00	
Neuroblastoma and other peripheral nervous cell tumours										
Total	USA	1443	53 716	1.43 (0.92–2.22)	1.25 (0.93–1.67)	1.13 (0.96–1.34)	1	**1.14 (1.00–1.30)**	**1.21 (1.02–1.44)**	1.03 (0.98–1.09)
	USA[d]	1505	57 569	1.38 (0.98–1.94)	1.16 (0.89–1.53)	1.11 (0.94–1.30)	1	1.13 (0.99–1.28)	**1.23 (1.04–1.45)**	1.02 (0.98–1.07)
	USA[e]	1043	48 844	1.25 (0.82–1.89)	1.25 (0.91–1.71)	**1.21 (1.00–1.47)**	1	1.15 (0.98–1.34)	1.18 (0.96–1.46)	1.01 (0.96–1.07)
	UK	1803	2386	1.21 (0.58–2.52)	0.93 (0.56–1.56)	0.83 (0.65–1.06)	1	1.18 (0.99–1.42)	1.27 (0.94–1.71)	1.02 (0.96–1.07)
Neuroblastoma and ganglioneuroblastoma	USA	1422	53 716	1.38 (0.88–2.15)	1.24 (0.92–1.67)	1.13 (0.95–1.34)	1	**1.15 (1.00–1.31)**	**1.22 (1.02–1.45)**	1.03 (0.98–1.09)
	USA[d]	1480	57 569	1.36 (0.96–1.93)	1.14 (0.87–1.51)	1.11 (0.94–1.30)	1	**1.13 (1.00–1.29)**	**1.24 (1.04–1.46)**	1.03 (0.98–1.08)
	USA[e]	1022	48 844	1.22 (0.80–1.86)	1.22 (0.89–1.68)	1.22 (1.01–1.47)	1	1.15 (0.99–1.35)	1.19 (0.97–1.47)	1.01 (0.96–1.07)
	UK	1785	2360	1.31 (0.61–2.78)	0.98 (0.58–1.64)	0.84 (0.66–1.07)	1	**1.19 (1.00–1.43)**	1.27 (0.94–1.71)	1.02 (0.96–1.07)
Other peripheral nervous cell tumours	USA	21	53 716	n/d	n/d	1.31 (0.39–4.39)	1	0.73 (0.24–2.25)	0.75 (0.16–3.57)	0.86 (0.56–1.32)
	UK	18	26	n/d	n/d	0.56 (0.08–3.86)	1	0.43 (0.05–3.79)	1.00 (0.02–50.40)	1.03 (0.61–1.75)

n/d, not determined as only 1 case.

[a]Data were adjusted for sex, period and region of birth. US data were further adjusted for gestational age, birth order, plurality, maternal age and race/ethnicity. This information was not available for UK data.

[b]Odds ratios whose 95% confidence intervals are above the null value (1) are bold.

[c]Considering birthweight as a continuous variable.

[d]Data unadjusted except for matching factors (state, year of birth and sex).

[e]Data unadjusted except for matching factors (state, year of birth and sex) and excluding cases and controls from the California dataset.

Table 5. Childhood cancers whose risk associates with birthweight in only one of the US or UK datasets

Cancer	Dataset[a]	Cases	Controls	Trend per 0.5 kg increase in birthweight[b]
Lymphomas and reticuloendothelial neoplasms				
Total	USA	1396	53 716	1.01 (0.96–1.07)
	UK	2020	2957	**1.06 (1.00–1.11)**
Hodgkin lymphomas	USA	431	53 716	1.02 (0.93–1.12)
	UK	823	1255	1.03 (0.95–1.12)
Non–Hodgkin lymphomas (except Burkitt lymphoma)	USA	549	53 716	0.99 (0.91–1.08)
	UK	847	1172	1.01 (0.93–1.10)
Burkitt lymphoma	USA	220	53 716	1.04 (0.91–1.18)
	USA[c]	232	57 569	1.03 (0.92–1.15)
	USA[d]	193	48 844	1.06 (0.94–1.20)
	UK	303	466	**1.28 (1.11–1.48)**
Miscellaneous lymphoreticular neoplasms	USA	142	53 716	1.04 (0.87–1.24)
	UK	15	19	1.57 (0.68–3.65)
Unspecified lymphomas	USA	54	53 716	1.00 (0.85–1.18)
	UK	32	45	0.89 (0.54–1.47)
Germ cell tumours, trophoblastic tumours and neoplasms of gonads				
Total	USA	527	53 716	**1.10 (1.01–1.20)**
	UK	785	1095	1.07 (0.99–1.16)
Intracranial and intraspinal germ cell tumours	USA	115	53 716	0.93 (0.77–1.12)
	USA[c]	127	57 569	0.90 (0.78–1.04)
	USA[d]	115	48 844	0.89 (0.76–1.04)
	UK	232	334	**1.19 (1.02–1.38)**
Malignant extracranial and extragonadal germ cell tumours	USA	131	53 716	**1.38 (1.17–1.64)**
	USA[c]	134	57 569	**1.36 (1.16–1.60)**
	USA[d]	83	48 844	**1.37 (1.11–1.68)**
	UK	229	325	1.00 (0.87–1.14)
Malignant gonadal germ cell tumours	USA	262	53 716	1.03 (0.92–1.17)
	UK	309	414	1.06 (0.93–1.22)
Gonadal carcinomas	USA	7	53 716	1.20 (0.64–2.25)
	UK	8	11	0.80 (0.24–2.68)
Other and unspecified malignant gonadal tumours	USA	12	53 716	1.03 (0.61–1.76)
	UK	7	11	0.88 (0.34–2.30)
Other malignant epithelial neoplasms and malignant melanomas				
Total	USA	366	53 716	1.02 (0.92–1.13)
	UK	563	847	**1.17 (1.07–1.29)**
Adrenocortical carcinomas	USA	20	53 716	1.39 (0.93–2.09)
	UK	39	57	1.09 (0.78–1.53)
Thyroid carcinomas	USA	141	53 716	1.03 (0.87–1.21)
	UK	107	174	1.12 (0.90–1.40)
Nasopharyngeal carcinomas	USA	10	53 716	0.97 (0.54–1.74)
	UK	28	43	1.60 (0.95–2.70)
Malignant melanomas	USA	114	53 716	1.02 (0.84–1.22)
	USA[c]	121	57 569	1.05 (0.90–1.24)
	USA[d]	108	48 844	1.02 (0.86–1.20)
	UK	152	215	**1.35 (1.12–1.64)**
Skin carcinomas	USA	3	53 716	0.90 (0.25–3.26)
	UK	102	62	1.12 (0.90–1.39)
Other and unspecified carcinomas	USA	78	53 716	0.94 (0.76–1.17)
	UK	135	196	1.02 (0.83–1.26)

(Continued)

Table 5. Continued

Cancer	Dataset[a]	Cases	Controls	Trend per 0.5 kg increase in birthweight[b]
Other and unspecified malignant neoplasms[e]				
Total	USA	77	53 716	**1.25 (1.01–1.56)**
	UK	152	235	0.99 (0.84–1.18)
Other specified malignant tumours	USA	11	53 716	**2.30 (1.36–3.88)**
	UK	24	32	1.08 (0.67–1.76)
Other unspecified malignant tumours	USA	31	53 716	1.23 (0.88–1.73)
	UK	128	203	0.98 (0.82–1.18)

[a]Data were adjusted for sex, period and region of birth. US data were further adjusted for gestational age, birth order, plurality, maternal age and race/ethnicity. This information was not available for UK data.

[b]Odds ratios (95% confidence intervals), considering birthweight as a continuous variable. Odds ratios whose 95% confidence intervals are above the null value (1) are bold.

[c]Data unadjusted except for matching factors (state, year of birth and sex).

[d]Data unadjusted except for matching factors (state, year of birth and sex) and excluding cases and controls from the California dataset.

[e]Cancers which were unclassifiable based on site and morphology combination were included in this group.

Table 6. Childhood cancers whose risk appears independent of birthweight

Cancer	Dataset[a]	Cases	Controls	Trend per 0.5 kg increase in birthweight[b]
Retinoblastoma				
Total	USA	660	53716	0.98 (0.91–1.06)
	UK	839	1116	0.98 (0.91–1.07)
Retinoblastoma – heritable	USA	162	53716	0.99 (0.85–1.16)
	UK	336	434	1.00 (0.88–1.13)
Retinoblastoma – nonheritable	USA	412	53716	0.98 (0.89–1.09)
	UK	503	682	0.97 (0.88–1.08)
Malignant bone tumours				
Total	USA	511	53716	1.03 (0.94–1.12)
	UK	720	1078	1.06 (0.97–1.16)
Osteosarcomas	USA	251	53716	1.02 (0.90–1.16)
	UK	390	583	1.04 (0.92–1.18)
Chondrosarcomas	USA	13	53716	1.21 (0.73–1.99)
	UK	12	17	0.92 (0.47–1.81)
Ewing tumour and related bone sarcomas	USA	202	53716	1.07 (0.93–1.22)
	UK	288	436	1.12 (0.97–1.29)
Other specified malignant bone tumours	USA	31	53716	1.12 (0.80–1.57)
	UK	15	21	1.02 (0.60–1.74)
Unspecified malignant bone tumours	USA	14	53716	***0.58 (0.35–0.95)***
	UK	15	21	0.93 (0.60–1.43)

[a]Data were adjusted for sex, period and region of birth. US data were further adjusted for gestational age, birth order, plurality, maternal age and race/ethnicity. This information was not available for UK data.

[b]Odds ratios (95% confidence intervals), considering birthweight as a continuous variable. Odds ratios whose 95% confidence intervals are below the null value (1) are bold italic.

particular risk relationship. Risks of other specified intracranial and intraspinal neoplasms were also only strongly associated with increasing birthweight in the UK (1.11 per 0.5 kg increase). However, there was a greater proportion of cases in this category in the UK (618/5702) compared with the USA (194/3561), suggesting classification differences and thereby tumour heterogeneity. For soft tissue sarcomas, risk was strongest for the embryonal rhabdomyosarcomas (USA: 1.25, UK: 1.12 per 0.5 kg increase). In both datasets, there was a reduced risk of hepatic tumours with increasing birthweight (Table 3). This inverse relationship was seen in each subcategory, though it was strongest for hepatoblastoma (USA: 0.73, UK: 0.81 per 0.5 kg increase).

Risk was also calculated by birthweight categories, and results generally mirrored those of the trend analyses

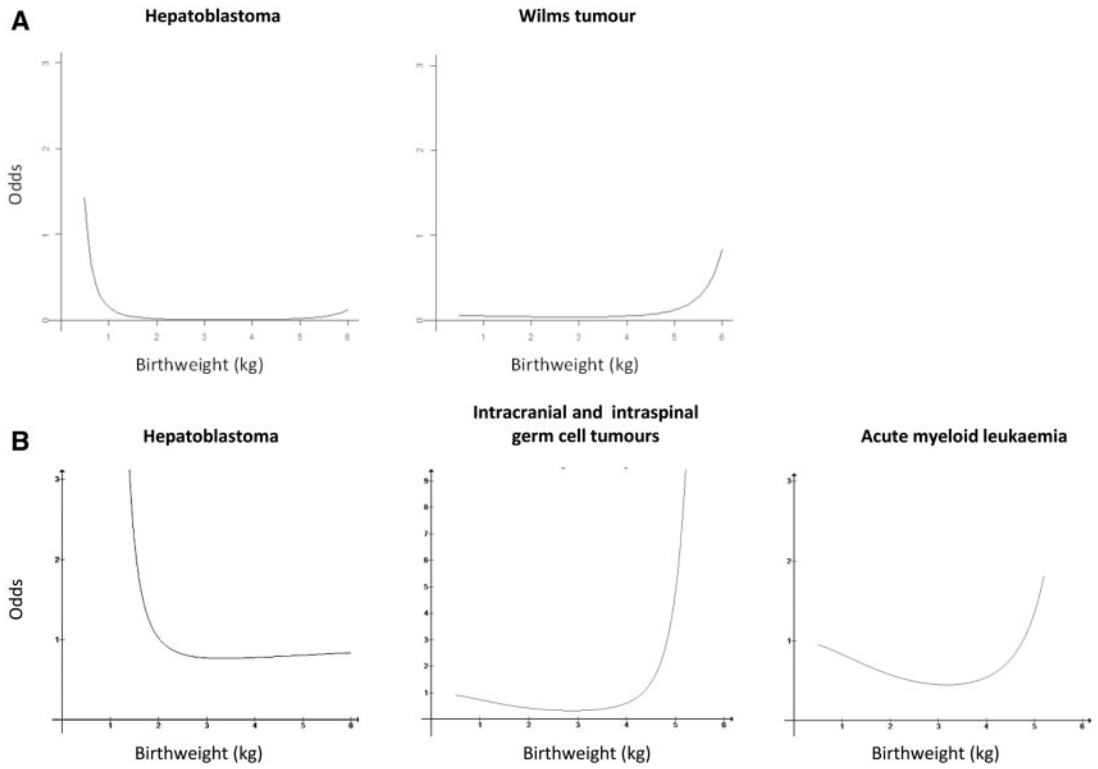

Figure 1. Childhood tumours that demonstrate non-linear risk relationships with birthweight. Fractional polynomial models were used to explore whether tumours displayed non-linear risk relationships with birthweight. Shown are tumours for which these fit better than the linear model. The plots illustrate the shape of the relationship described by the best-fit polynomial models for (A) US data: hepatoblastoma (log x and x3 terms) and Wilms tumour (x3 and x3 log x terms); and (B) UK data: hepatoblastoma (x2 term), intracranial and intraspinal germ cell tumours (x3 term) and acute myeloid leukemia (x2 and x3 terms).

shown in Table 3 (Supplementary Table S1, available as Supplementary data at *IJE* online). For neuroblastoma, risk in both datasets was increased when considering birthweight as a continuous variable, but was particularly strong for high birthweight babies, especially in the USA (Table 4). Analysis of US data without adjustment for potential confounders made little difference to calculated risks (Table 4). Neuroblastoma primarily affects young children, with approximately 85% diagnosed at $\leq$4 years of age.[1] This age group is disproportionately represented in the US dataset because of the Californian contribution (Table 1). Omitting California data from the analysis weakened risk associations with high birthweight (Table 4), suggesting that risk of neuroblastoma is particularly increased in younger children.

Childhood cancers that associate with birthweight in either dataset

Slight discrepancies between datasets were observed for some tumour types (Table 5). For lymphomas, strong risk associations were observed with increasing birthweight in the UK, particularly for Burkitt lymphoma (1.28 per 0.5 kg increase), whereas risk associations for the USA remained weak regardless of adjustment for potential confounders and omission of the California dataset. Each 0.5 kg increase in birthweight was also associated with increased risk of total germ cell tumours, but the strength of the association for different tumour subtypes varied between datasets. Intracranial and intraspinal germ cell tumours were most strongly associated with increasing birthweight in the UK (1.19 per 0.5 kg increase). Risk associations for this tumour type in the USA were weaker, regardless of confounder adjustment or exclusion of the California dataset. Malignant extracranial and extragonadal germ cell tumour risk, on the other hand, was most evident in the USA (1.38 per 0.5 kg increase), and remained so without confounder adjustment (1.36 per 0.5 kg increase) or minus the California dataset (1.37 per 0.5 kg increase). For other malignant epithelial neoplasms and malignant melanomas, a strong association with increasing birthweight was observed in the UK, driven by malignant melanomas (1.35 per 0.5 kg increase). This was not observed in the USA, irrespective of confounder adjustment or exclusion of California's data. Increased risk of other and unspecified malignant neoplasms was strongest for the USA, but numbers in both datasets were small and the tumours included are heterogeneous. These dataset-specific

results were also generally observed when considering risk by birthweight category (Supplementary Table S2, available as Supplementary data at *IJE* online).

Childhood cancers that appear to be independent of birthweight

In contrast to the above childhood cancers, we did not observe strong associations between increasing birthweight and risk of retinoblastomas or malignant bone tumours, in either dataset (Table 6). Risks remained weak for both of these tumour types when birthweight was considered categorically (Supplementary Table S3, available as Supplementary data at *IJE* online).

Complex risk associations between some childhood cancers and birthweight

Finally, we tested whether fractional polynomial regression models fitted the data better than simple linear ones. Although a linear risk relationship best described associations for the majority of tumours, non-linear models were a better fit for some disease subtypes (Figure 1). In both datasets, low birthweight was particularly associated with hepatoblastoma risk. In contrast, a marked risk association with high birthweight was noted for Wilms tumour in the USA and intracranial and intraspinal germ cell tumours in the UK. Although AML was not associated with birthweight categorically or linearly in either dataset, a U-shaped association was observed within the UK.

Discussion

Here we have shown that birthweight is a risk factor for childhood leukaemia, CNS tumours, renal tumours, soft tissue sarcomas and hepatic tumours, and may also associate with risk of neuroblastoma, lymphoma, germ cell tumours and other malignant neoplasms/melanomas. Risk appears to be specific to subtypes of each of these tumours. In total, the associated subtypes constitute roughly half of all childhood cancers.

Results in relation to other studies

Childhood leukaemia

Risk relationships between childhood leukaemia and birthweight are well characterized.[3,4,19] Our results confirm that high birthweight increases risk of ALL, but suggest that the relationship with AML may not be straightforward. The U-shaped risk association observed within the UK, which was also noted in a meta-analysis,[3] was not evident in the USA. Stratification of US data by age at diagnosis did reveal a strong U-shaped association for children diagnosed when aged 5–14 years [OR 3.27 (95% CI 1.34, 7.96) for <2.0 kg; 1.63 (1.13, 2.36) for ≥4.0 kg; compared with the 3.00–3.49 kg reference group], but not for those aged ≤4 years. This is based on low case numbers, but indicates that variations in age distribution between datasets may influence the observed risks. Another consideration is confounding by DS, which is independently associated with low birthweight[20] and risk of myeloid leukaemia.[21] In our study, cases with DS were excluded from the US data, but not from the UK data due to incomplete recording of DS on UK birth records. Association with low birthweight decreased when known DS cases were omitted from the UK, and increased when DS cases were included in the USA—with negligible effect on associations with high birthweight (data not shown). This may indicate that the increased risk of AML observed for low birthweight babies may be attributable to DS.

Our results also indicate that birthweight is not a strong risk factor for infant leukaemias. We previously reported that birthweight specifically increases risk of leukaemias with high hyperdiploidy and t(1;19) translocations,[4] and others have also observed differences in risk according to cytogenetic feature.[19] These chromosomal abnormalities are underrepresented in infant leukaemias,[22] which may explain why birthweight does not significantly influence risk for this age group.

Childhood CNS tumours, renal tumours and neuroblastoma

Although results of previous individual studies of birthweight and risk of CNS tumours, renal tumours and neuroblastoma have varied significantly, meta-analyses of these tumour types[7–9] generally align with our results. However, the comparison of two independent datasets in our study has highlighted potential factors that may help explain previous inconsistencies.

For CNS tumours, although we and others[7] find that high birthweight associates with risk of astrocytomas but not ependymomas, the evidence for CNS embryonal tumours is more varied. Even within our own study, we observed variation in risk between US and UK datasets. Given that these embryonal tumours are exceptionally heterogeneous,[23] this inconsistency may be due to varying proportions of tumour subgroups within datasets. However, as discussed below, our results also indicate that risk of this subtype is influenced by adjustment for gestational age, which may also explain the variation observed in the literature.

A meta-analysis of Wilms tumour concluded an increased risk in high birthweight babies.[9] In our study,

risk was greatest among the very high birthweight in the USA, where 5% of cases weighed >4.5 kg at birth. In the UK, risk increased less dramatically (i.e. linearly) with birthweight, with only 3% of cases weighing >4.5 kg. Thus the proportion of cases with very high birthweights may influence the shape of the risk relationship. Wilms tumour is associated with a number of overgrowth syndromes that are characterized by very high birthweight.[24] Although we did not have the clinical data to explore this, it is possible that cases with these syndromes are more prevalent among our US population, driving the strong association with very high birthweight.

For neuroblastoma, meta-analyses have suggested a risk association with low birthweight,[8] although our study did not find evidence of this. Of note, we observed stronger risk associations between high birthweight and neuroblastoma when the majority of cases were <5 years old. Results may therefore differ because of differences in the age distribution across studies.

Childhood lymphoma

Literature on risk associations between birthweight and childhood lymphoma has been particularly contradictory. A recent meta-analysis concluded no significant risk associations with birthweight,[25] but studies have differed markedly with respect to disease stratification and adjustment for confounders.[19,25] Furthermore, lymphoma classification has seen significant uncoordinated changes over the past 60 years,[26,27] which has undoubtedly impacted on the results of these studies. Here we have considered the largest number of lymphomas to date, with over five times as many cases as the previous largest single study.[28] We observe that risk of lymphoma strongly associates with high birthweight within the UK, particularly for Burkitt lymphoma. Why this association is weaker in the USA is unclear. There is a slightly younger age distribution among US cases (35% aged 1–4 years, 37% 5–9 and 27% 10–14) compared with the UK (27% 1–4, 42% 5–9 and 31% 10–14), which might suggest that earlier onset lymphomas are driven by factors other than birthweight. It may also be that, like the leukaemias,[4,19] risk is strongest for particular cytogenetic subtypes, and their crude and possibly inconsistent grouping into Hodgkin, Burkitt and other non-Hodgkin lymphomas masks true risk associations. Furthermore, our results may be confounded by Epstein–Barr virus (EBV) infection. EBV is a known causative agent of Burkitt lymphoma[29] and is associated with 15–20% of cases in North America and Europe.[30] Although we did not have information on the EBV status of the cancers included in our analysis, measures of EBV seroprevalence among the childhood population during our study period report a higher rate in the USA (64% of 12–14-year-olds)[31] compared with the UK (54% of 10–14-year-olds).[32] One could therefore speculate that our data indicate that risk association with birthweight is more significant for non-EBV-associated lymphomas.

Thus although we conclude that birthweight is a risk factor for childhood lymphoma, further studies considering age at diagnosis, diagnostic subgroup and EBV status are warranted.

Rare childhood cancers

For the less common childhood cancers, low case numbers have hampered previous investigations. Results of limited studies exploring soft tissue sarcomas[28,33–35] and germ cell tumours[36–40] are inconsistent, and to date there has been no investigation into risk associations between birthweight and other malignant neoplasms/melanomas in children. Our data indicate that birthweight is a risk factor for subsets of these diseases, but that some of these relationships may be complex and possibly influenced by other factors.

We found that increasing birthweight associates with risk of soft tissue sarcomas, specifically the embryonal rhabdomyosarcomas. Risk relationships with malignant melanomas and germ cell tumours appear to be more complex, with contrasting results between our datasets that are not explained by variation in gestational age, maternal age, plurality, birth order or maternal race/ethnicity. Classification issues may explain some of these discrepancies, particularly for malignant melanomas. These tumours can be difficult to distinguish from benign growths in children,[1] so it is possible that some misclassified benign melanomas were included in our analysis, thus skewing results. There may also be genetic or geographical factors that make the UK population more susceptible to increased risk of disease in high birthweight babies. Of note, high birthweight was recently shown to associate with risk of malignant melanoma in adults in a UK-based study.[41]

The pronounced non-linear association between intracranial and intraspinal germ cell tumours and high birthweight, observed only in the UK, is likely to be driven by the high proportion of cases with very high birthweights (3.0% >4.5 kg) compared with controls (0.3%), which was not observed in the USA (3.5% cases >4.5 kg, compared with 2.2% controls). The reason for this difference is unclear. We did note a higher proportion of female cases of this tumour type in the UK (41.1%) compared with the USA (33%), and since birthweight has been shown to affect risk in a sex-dependent manner for the haematological malignancies,[19] the higher risk association seen in the UK may indicate that risk is more prominent in females. Dataset differences in sex distribution were not observed for malignant extracranial and extragonadal germ cell tumours (data not shown), which only displayed a risk

association with birthweight in the USA. Although germ cell tumours have a common cellular origin, they develop at diffuse sites with variation in histology, genetics and biology.[42] If these tumour phenotypes have differential risk relationships with birthweight, then varying proportions within each dataset may explain our apparently contrasting results.

For hepatoblastoma, our finding of a non-linear marked association with low birthweight is likely to be driven by the relatively high proportion of babies with birthweights less than 2.0 kg (15.9% and 8.7% for the USA and the UK, respectively, Table 2), which would align with previously reported increased risk of hepatobastoma in very low birthweight babies.[43]

Strengths and limitations of the study

Our study was limited by the lack of information on gestational age, maternal age, plurality, birth order and maternal race/ethnicity for the UK data. As such, we were not able to adjust both datasets for the same covariates. However, comparison of results between datasets demonstrated a striking concordance for the majority of tumours, strongly suggesting that birthweight influences the risk of many childhood cancers independently of these variables. Where we did observe differences in risk between datasets, reanalysis of unadjusted US data had little impact (Table 5). These differences may therefore indicate confounding by other factors and/or an impact of tumour heterogeneity or classification differences, as discussed above. It must also be acknowledged that, given the large number of tests performed, some of our findings may be due to chance, and should therefore be interpreted with caution.

Interpretation

We were able to consider gestational age in US, but not UK, data. For the majority of tumours that displayed an increased risk with increasing birthweight in both datasets (Table 3), ORs were slightly higher for US data. This suggests that although the weight of the baby at birth is important, risk of cancer is principally related to the rate at which the fetus grows. Similar observations have been reported for ALL.[44]

In contrast, CNS tumours displayed lower ORs for US data (adjusted) compared with UK data (unadjusted) (Table 3). This is most apparent for the intracranial and intraspinal embryonal tumours, where a strong risk association was only observed for unadjusted US risk estimates. Therefore, for CNS tumours, weight of the newborn may have a greater impact on risk than the rate of fetal growth. This would align with previous reports illustrating that risk of childhood brain tumours increases significantly with increasing head circumference at birth,[45,46] and suggests that risk may be driven by organ size and pool of susceptible cells at birth.

The biological mechanisms linking fetal growth/size and cancer risk are unknown. Since we observe significant risk association with a diversity of otherwise unrelated tumours, there may be a causal relationship with the number, size or proliferative potential of cells in the relevant tissue of the neonate. The number and proliferative potential of muscle stem cells,[47] neuronal progenitor cells[48] and haematopoietic stem cells (HSCs)[49,50] have all been shown to positively correlate with birthweight. Since these cells are particularly susceptible to oncogenic mutation, a greater proportion of them in a faster-growing or larger fetus may facilitate an increased risk of cancer.

This notion is also supported by observations in children with overgrowth disorders such as Beckwith-Wiedemann syndrome (BWS). These babies, characterized by increased fetal growth rate and/or increased organ size, are prone to a wide range of cancers including Wilms tumour, hepatic tumours, rhabdomyosarcomas, neuroblastoma and leukaemia.[51] BWS is caused by overexpression of the insulin-like growth factor (*IGF*) 2 gene, and with the established role of IGFs in many adult cancers, it is likely that these high levels contribute to the onset of cancer in these children. Since IGF levels are also increased in heavier babies without these overgrowth syndromes, there may be a more general association between levels of IGF in the neonate and risk of childhood cancer.[5,6,19] Further support comes from a recent study describing how babies born with congenital IGF1 deficiency or insensitivity to growth hormones are protected against subsequent risk of developing cancer.[52] The discovery of polymorphic variants of genes in the IGF axis that associate with risk of childhood ALL[53] suggests that there may be a genetic explanation for the increased risk of cancer in children with high birthweights, though it remains to be seen whether this is the case for the diversity of cancers described in the present study. Other postulated mechanisms include exposure of faster-growing/bigger babies to elevated levels of estrogen *in utero*, as well as other genetic polymorphisms or epigenetic signatures that associate with both fetal growth/birthweight and cancer risk, discussed in more detail elsewhere.[19]

Whether any of these mechanisms would explain the risks observed with low birthweight is unclear. Hepatoblastoma has been associated with very low birthweight in other studies, and the frequent medical interventions often required for these infants and/or maternal smoking may be responsible.[43] However, the graded relationship that we observe with decreasing birthweight

perhaps implies the contribution of factors other than medical intervention. Our fractional polynomial analysis suggests that risk relationships for Wilms tumour, intracranial and intraspinal germ cell tumours and AML may also be complex. Each of these relationships may reflect differences in the contribution of specific cell types to tissue growth and development. For example, U- and J- shaped relationships have been reported between birthweight and number of HSCs within umbilical cord blood.[47] If similar relationships exist for other types of stem cells, this may offer a potential explanation of these more complex risk associations.

Here we have presented evidence that risk association between birthweight and some childhood cancers may be influenced by age and sex, as well as population and geographical parameters. We also suggest that risk may be specific to tumour subgroups. Finally, we show that risk of some cancers appears to be independent of birthweight, suggesting that they have distinct aetiologies. These details may be important for future studies aimed at understanding the biological mechanisms underlying the intriguing relationship between growth *in utero* and cancer in childhood.

Importance and public health impact

Between the 1970 s and the late 1980 s, birthweights gradually increased in several developed countries.[54] Paralleling these trends, the incidence of childhood cancer steadily rose, with average increases of 1% per year (1974 to 1991) in the USA[55] and 1.1% per year (1978 to 1997) in Europe.[56] Since the 1990 s, however, average birthweights have begun to decrease. For example, babies born in the USA in 1990 weighed on average 3.44 kg, but only 3.39 kg in 2005.[57] Concomitantly, recent figures from the UK suggest that incidence rates of childhood cancer have plateaued since the early 2000 s.[58] In light of the results presented here, one could speculate that these changes in cancer incidence rates may be related to changes in birthweight trends.

The proportion of newborns with a high birthweight (≥4 kg) in 2012 was approximately 8% in the USA[59] and 11% in England and Wales.[60] Our results would therefore suggest that currently, about one-tenth of newborns have an increased risk of developing cancer in childhood. However, we are now in the midst of a global obesity epidemic, with a recent report that adult obesity has risen so dramatically since 2000 that one in nine people older than 20 years was clinically obese in 2008.[61] This means that the number of women of childbearing age who are obese is on the increase. Since mothers who are overweight/obese are up to twice as likely to give birth to babies weighing ≥4 kg,[62] birthweights and risks of childhood cancer may once again climb, and with this the necessity to understand the biological mechanisms that drive these risk associations.

Supplementary Data

Supplementary data are available at *IJE* online.

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M.M. and L.S. conceived, designed and supervised the study. K.O., M.M., S.C., B.M., C.M., P.R. and L.S. obtained funding; K.O., M.M., K.B. and L.S. analysed and interpreted the data; T.V. provided administrative, technical and material support; K.B., S.P. and L.S. performed the statistical analysis; and K.O. drafted the manuscript. K.O. and M.M. contributed equally to this work and share first authorship. All authors critically revised the manuscript for important intellectual content, and contributed to and approved the final version. All authors also had full access to the data in the study, and each takes responsibility for the integrity of the data and the accuracy of the data analysis. K.O., M.M. and L.S. are the guarantors of the study.

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