Fetal growth and the risk of childhood non-CNS solid tumours in Western Australia

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METHODS

Using population-based linked health data, we investigated whether the risk of certain childhood non-CNS solid tumours (n = 186) was associated with intra-uterine growth. The risk of retinoblastoma and rhabdomyosarcoma, but not other tumour types, was positively associated with increased growth, suggesting a possible role of fetal growth factors. Larger studies are needed.

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RESULTS

The sex distribution varied by type of tumour, with a higher proportion of males than females with neuroblastoma and retinoblastoma, more than half of which with were diagnosed before 2 years of age. The proportion of first-born children was higher in each tumour group than in the non-case group (Table 1). The risk of retinoblastoma (HR: 0.54) was lower among girls than boys (Table 2). Overall, there was little evidence of an
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association between the three IUG measures and risk of neuroblastoma or Wilms’ tumour. There appeared to be weak positive associations between POBW and retinoblastoma (HR: 1.22) and rhabdomyosarcoma (HR: 1.33) (Table 2). Similarly, POBL appeared to be positively associated with retinoblastoma (HR: 1.26) and POWFL with rhabdomyosarcoma (HR: 1.41) (Table 2), though few associations were statistically significant.

As in our approach with childhood ALL (Milne et al, 2007), CNS tumors and lymphomas (Milne et al, 2008), we aimed to distinguish an effect of high birth weight per se and one with accelerated growth. We restricted the univariate regression analysis of POBW to, in turn, children with birth weights below two commonly used definitions of high birth weight: >3500 and >4000 g. The positive associations observed between POBW and retinoblastoma and rhabdomyosarcoma were also observed among children with birth weights <3500 and <4000 g retinoblastoma (HR: 1.39, 95% CI 0.82–2.36 and HR: 1.32, 95% CI 0.89–1.95, respectively); and rhabdomyosarcoma (HR: 1.53, 95% CI 0.82–2.86 and HR: 1.55, 95% CI 1.00–2.40, respectively).

DISCUSSION

Our measures of the appropriateness of fetal growth – POBL, POBW and POWFL – are independent of gestational age and take account of the major non-pathological determinants of IUG. As with ALL (Milne et al, 2007) and lymphomas (Milne et al, 2008), there was a positive association between at least one measure of IUG and risk of retinoblastoma and rhabdomyosarcoma. We found no evidence of an association between IUG and risk of neuroblastoma and, unlike previous studies (Leisenring et al, 1994; Yeazel et al, 1997; Schuz et al, 2001), we found no association between IUG and the risk of Wilms’ tumour.

Growth is a mixture of skeletal growth – tending to be expressed as increased height; and somatic growth, which may be proportionate (ie, a large child, but with a normal body mass index), or disproportionate (increased soft tissue with a raised body mass index/POWFL). Insulin-like growth factors play a major role in regulating the normal growth and differentiation of cells and tissues during fetal development (LeRoith et al, 1991). Some tumours produce IGF-I, IGF-II or their binding proteins, or possess IGF receptors (Campbell and Novak, 1991; Antoniades et al, 1992; Hirschfeld and Helman, 1994; Boule et al, 1998). IGF-I, in particular, inhibits the process of programmed cell death in both normal and DNA-damaged cells (Barres et al, 1992; Baserga et al, 1997a). The mitotic properties of IGFs, coupled with their ability to inhibit cell death, are thought to enhance tumour growth (Barsera et al, 1997b; Werner and Le Roith, 2000; Bentov and Werner, 2004; Pollak et al, 2004). Different tumours are likely to have different underlying genetic predispositions, which in turn are likely to be reflected in different patterns of growth, which may partly explain the associations we observed.

This study has some important strengths. Examining risk associated with the appropriateness of IUG allows a more detailed exploration of this relationship than using birth weight alone or birth weight with adjustment for gestational age. We were able to explore associations between some specific solid cancers of childhood and three distinct aspects of IUG: POBW, POBL and POWFL. The z-scores for each of these were modeled appropriately as continuous variables and this method obviated the need to assign an arbitrary cutoff for ‘high birth weight’. Being a population-based, record-linkage study, neither selection bias nor recall bias would have affected our results.

There were small numbers of cases in this study and many results were only suggestive of an association; however, our findings are consistent with literature describing biologically plausible mechanisms for associations between increased fetal growth and risk of some non-CNS solid tumours. The persistence of our results when the analysis was restricted to children without high birth weight further supports an association with accelerated growth, rather than high birth weight per se.

We recommend for future studies, the use of measures of the appropriateness of IUG rather than birth weight alone, particularly

Table 1  Descriptive characteristics of non-CNS solid tumours in children aged 0–14 years in Western Australia

| Sex | Age at diagnosis | Birth order | POBW | POBL | POWFL |
|-----|-----------------|-------------|------|------|-------|
|     | N (%)           | N (%)       | N (%)| N (%)| N (%) |
| Non-cases | 576352 | 293766 | 282586 | 295903 | 280449 |
| Neuroblastoma | 69 | 40 (58.0) | 29 (42.0) | 39 (56.5) | 30 (43.5) |
| Retinoblastoma | 38 | 25 (65.8) | 13 (34.2) | 23 (60.5) | 15 (39.5) |
| Wilms’ tumour | 52 | 25 (48.1) | 27 (51.9) | 20 (38.5) | 32 (61.5) |
| Rhabdomyosarcoma | 27 | 13 (48.2) | 14 (51.8) | 9 (33.3) | 18 (66.7) |

Non-cases = non-central nervous system; POBW = proportion of optimal birth weight; POBL = proportion of optimal birth length; POWFL = proportion of optimal weight for length.

Table 2  Cox univariate regression analysis of non-CNS solid tumours in children aged 0–14 years in Western Australia

| Female sex | Not first born | POBW z-score | POBL z-score | POWFL z-score |
|------------|---------------|--------------|--------------|---------------|
|            | HR CI         | HR CI        | HR CI        | HR CI         |
| Neuroblastoma | 0.75 (0.47,1.22) | 0.98 (0.61,1.57) | 1.09 (0.86,1.38) | 1.04 (0.82,1.32) | 1.07 (0.85,1.36) |
| Retinoblastoma | 0.54 (0.28,1.06) | 0.86 (0.46,1.64) | 1.22 (0.90,1.66) | 1.26 (0.92,1.72) | 1.18 (0.86,1.60) |
| Wilms’ tumour | 1.12 (0.65,1.94) | 0.80 (0.46,1.39) | 1.10 (0.84,1.44) | 0.93 (0.71,1.22) | 1.08 (0.82,1.42) |
| Rhabdomyosarcoma | 1.12 (0.53,2.38) | 0.75 (0.35,1.62) | 1.33 (0.93,1.90) | 0.99 (0.68,1.44) | 1.41 (0.98,2.01) |

HR = hazard Ratio; CI = 95% confidence interval; POBW = proportion of optimal birth weight; POBL = proportion of optimal birth length; POWFL = proportion of optimal weight for length.
in large collaborative studies that can examine these relationships with greater power.

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