Short Communication

Birth and parental characteristics and risk of neuroblastoma in a population-based Norwegian cohort study

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In this population-based Norwegian cohort study (2.1 million children), the impact of birth and parental characteristics on the risk of neuroblastoma (178 cases) was evaluated. In children below the age of 18 months, there was an increased neuroblastoma risk among those with congenital malformations and suggestion of increased risk when the mother had pre-eclampsia.

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Neuroblastoma is the most common cancer in children less than 1 year of age, and is the third most common malignancy in childhood (below 5 years of age) in the United States (Goodman et al, 1999). The incidence of neuroblastoma has increased in some European countries during 1978–1997 (Kaatsch et al, 2006; Spix et al, 2006), possibly influenced by changes in identification and reporting of the disease over time. Although there has been substantial improvement in prognosis of well-defined subsets of patients in the past few decades, the long-term survival for children with high-risk disease is still less than 40% (Maris et al, 2007).

Neuroblastoma is an embryonal tumour that originates from primordial neural crest cells that eventually develop into the sympathetic nervous system (SNS) and the adrenal medulla. The tumour almost exclusively occurs in infants and young children. About 50% of the tumours originate in the adrenal gland, another 20% in other areas of the abdomen and about 30% in the sympathetic ganglia in the neck, thorax and pelvis (Huddart and Mann, 1991; Buck et al, 2001). The most frequent genetic abnormality found in neuroblastoma is the amplification of the MYCN protooncogene, but also other genetic abnormalities have been identified (Maris et al, 2007).

Relatively little is known about the aetiology of neuroblastoma. The peak incidence during early childhood indicates that prenatal and perinatal factors may play an important role in its pathogenesis, but the evidence is rather limited and inconclusive (Hamrick et al, 2001; Schuz et al, 2001). In this study, we aimed to evaluate the impact of birth and parental characteristics on the risk of neuroblastoma, both adrenal and non-adrenal, in a large population-based Norwegian cohort study, using data from the medical birth and cancer registries of Norway.

MATERIALS AND METHODS

Study subjects

The Medical Birth Registry of Norway (MBRN) is population-based and contains information on all births in Norway since 1967, defined as all live births and reported foetal deaths of 16 complete weeks of gestation or more. Each record contains information on demographic variables, pregnancy, delivery and the newborn (Irgens, 2000). Data on all deaths registered by Statistics Norway are routinely linked to the birth records. Medical Birth Registry of Norway includes a unique identification number assigned to all live-born children in Norway as well as parents.

Since 1953, the Cancer Registry of Norway (CRN) has received information on all cancer patients in the population. The reporting system is based on pathology and cytology reports, clinical records and death certificates, and provides information about site, histological type and stage of disease at the time of diagnosis (The Cancer Registry of Norway, 2008). Through 1992, registration was based on a modified version of ICD-7. Since 1993, ICD-O has been the basis for coding.

All live-born children in Norway during the period 1967–2004 (n = 2,127,452) were defined as our study cohort. However, twins, triplets and quadruplets were excluded from the analyses. The personal identification number was used to link the two registries to identify all cases of neuroblastoma in children below 15 years of age. For each child, only the first histologically verified malignant tumour was included in the study. All histologically confirmed neuroblastoma in the SNS were included. Neuroblastomas in the central nervous system and in the eye were excluded. Ganglioneuroblastoma and ganglioneuromas were excluded as well. Each person was followed up from date of birth until 15 years of age, emigration, cancer diagnosis (any site), death or until 31 December 2004. Screening for neuroblastoma has never been introduced in Norway.
# Table 1: Relative risk (RR) of neuroblastoma (adrenal and non-adrenal) with 95% confidence intervals (CIs) obtained in Cox regression analyses with age as the time variable, univariate

|                          | Adrenal medulla | Non-adrenal | All          |
|--------------------------|-----------------|-------------|--------------|
|                          | N               | RR (95% CI) | N            | RR (95% CI) | N            | RR (95% CI) |
| Sex                      |                 |             |              |             |              |              |
| Male                     | 44              | 1.0 Referent| 50           | 1.0 Referent| 94           | 1.0 Referent|
| Female                   | 39              | 0.9 (0.6 –1.4) | 45          | 1.0 (0.6 –1.4) | 84          | 0.9 (0.7 –1.3) |
| Season of birth          |                 |             |              |             |              |              |
| Winter                   | 19              | 1.0 Referent| 22           | 1.0 Referent| 41           | 1.0 Referent|
| Spring                   | 21              | 1.0 (0.5 –1.8) | 22         | 0.9 (0.5 –1.6) | 43         | 0.9 (0.6 –1.4) |
| Summer                   | 14              | 0.7 (0.3 –1.4) | 32         | 1.4 (0.8 –2.4) | 46         | 1.1 (0.7 –1.8) |
| Autumn                   | 29              | 1.6 (0.9 –2.8) | 19         | 0.9 (0.5 –1.6) | 48         | 1.2 (0.8 –1.8) |
| Birth year               |                 |             |              |             |              |              |
| 1967–1976                | 15              | 1.0 Referent| 34           | 1.0 Referent| 49           | 1.0 Referent|
| 1977–1986                | 31              | 2.5 (1.4 –4.7) | 22         | 0.8 (0.5 –1.4) | 53         | 1.3 (0.9 –2.0) |
| 1987–1996                | 23              | 1.6 (0.9 –3.1) | 24         | 0.8 (0.5 –1.3) | 47         | 1.0 (0.7 –1.5) |
| 1997–2004                | 14              | 1.7 (0.8 –3.6) | 15         | 0.9 (0.5 –1.6) | 29         | 1.1 (0.7 –1.8) |
| Test for trend           |                 | P = 0.07    | P = 0.4      | P = 0.2      |              |              |
| Gestational age (weeks)  |                 |             |              |             |              |              |
| <37                      | 3               | 0.8 (0.3 –2.7) | 2          | 0.5 (0.1 –2.0) | 5          | 0.6 (0.3 –1.6) |
| 37–39                    | 25              | 1.0 (0.6 –1.6) | 27         | 1.0 (0.6 –1.5) | 52         | 1.0 (0.7 –1.4) |
| 40–41                    | 38              | 1.0 Referent| 43          | 1.0 Referent| 81         | 1.0 Referent|
| 42+                      | 16              | 1.5 (0.8 –2.7) | 14         | 1.2 (0.6 –2.1) | 30         | 1.3 (0.9 –2.0) |
| Birth weight (g)         |                 |             |              |             |              |              |
| 500–2499                 | 3               | 1.3 (0.4 –4.5) | 0          | 0.0 (0.0)     | 3          | 0.6 (0.2 –1.9) |
| 2500–2999                | 8               | 1.1 (0.5 –2.5) | 11         | 1.2 (0.6 –2.4) | 19         | 1.2 (0.7 –2.0) |
| 3000–3499                | 22              | 1.0 Referent| 28          | 1.0 Referent| 50         | 1.0 Referent|
| 3500–3999                | 32              | 1.3 (0.8 –2.2) | 36         | 1.1 (0.7 –1.9) | 68         | 1.2 (0.7 –1.7) |
| 4000–4999                | 15              | 1.4 (0.7 –2.1) | 18         | 1.3 (0.8 –2.4) | 33         | 1.4 (0.7 –1.6) |
| 4500–6300                | 2               | 0.8 (0.2 –3.4) | 1          | 0.3 (0.0 –2.3) | 3          | 0.5 (0.2 –1.7) |
| Test for trend           |                 | P = 0.6      | P = 0.2      | P = 0.5      |              |              |
| Birth length (cm)        |                 |             |              |             |              |              |
| 40–49                    | 22              | 0.6 (0.4 –1.2) | 25         | 0.8 (0.5 –1.5) | 47         | 0.7 (0.5 –1.1) |
| 50                       | 23              | 1.0 Referent| 20          | 1.0 Referent| 43         | 1.0 Referent|
| 51                       | 7               | 0.3 (0.1 –0.8) | 21         | 1.2 (0.6 –2.2) | 28         | 0.7 (0.5 –1.2) |
| 52                       | 13              | 0.8 (0.4 –1.6) | 13         | 0.9 (0.5 –1.8) | 26         | 0.8 (0.5 –1.4) |
| 53–60                    | 13              | 0.8 (0.4 –1.5) | 13         | 0.9 (0.4 –1.8) | 26         | 0.8 (0.5 –1.3) |
| Test for trend           |                 | P = 0.4      | P = 0.4      | P = 0.2      |              |              |
| Head circumference (cm)   |                 |             |              |             |              |              |
| <35                      | 18              | 1.1 (0.6 –1.9) | 19         | 1.2 (0.7 –2.1) | 37         | 1.1 (0.7 –1.7) |
| 35–36                    | 30              | 1.0 Referent| 29          | 1.0 Referent| 59         | 1.0 Referent|
| 37+                      | 17              | 1.5 (0.8 –2.7) | 12         | 1.1 (0.6 –2.2) | 29         | 1.3 (0.8 –2.0) |
| Test for trend           |                 | P = 0.3      | P = 1.0      | P = 0.5      |              |              |
| Congenital malformations  |                 |             |              |             |              |              |
| No                       | 78              | 1.0 Referent| 92          | 1.0 Referent| 170         | 1.0 Referent|
| Yes                      | 5               | 3.2 (1.3 –7.8) | 3          | 1.6 (0.5 –5.1) | 8          | 2.3 (1.2 –4.8) |
| Material age (years)     |                 |             |              |             |              |              |
| <20                      | 1               | 0.2 (0.0 –1.6) | 6          | 1.2 (0.5 –2.9) | 7          | 0.7 (0.3 –1.6) |
| 20–24                    | 26              | 1.0 (0.6 –1.7) | 25         | 0.9 (0.5 –1.5) | 51         | 1.0 (0.7 –1.4) |
| 25–29                    | 34              | 1.0 Referent| 36          | 1.0 Referent| 70         | 1.0 Referent|
| 30–34                    | 35              | 0.7 (0.4 –1.2) | 18         | 0.8 (0.4 –1.4) | 33         | 0.7 (0.5 –1.1) |
| 35+                      | 7               | 0.7 (0.3 –1.6) | 10         | 0.9 (0.5 –1.9) | 17         | 0.8 (0.5 –1.4) |
| Test for trend           |                 | P = 0.4      | P = 0.6      | P = 0.4      |              |              |
| Parity                   |                 |             |              |             |              |              |
| 1                        | 37              | 1.0 Referent| 38          | 1.0 Referent| 75         | 1.0 Referent|
| 2–3                      | 37              | 0.8 (0.5 –1.3) | 45         | 1.0 (0.6 –1.5) | 82         | 0.9 (0.6 –1.2) |
| 4–5                      | 8               | 1.3 (0.6 –2.9) | 8          | 1.3 (0.6 –2.8) | 16         | 1.3 (0.8 –2.3) |
| 6+                       | 1               | 1.1 (0.2 –8.3) | 2          | 2.2 (0.5 –9.2) | 3          | 1.7 (0.5 –5.4) |
| Test for trend           |                 | P = 0.8      | P = 0.9      | P = 0.9      |              |              |

**Total no. of person-years**

- Adrenal medulla: 12 986 975
- Non-adrenal: 12 315 885
- All: 25 302 860

Epidemiology
The statistical package SPSS (SPSS Inc., 2006) was used for estimating RR of neuroblastoma with 95% confidence intervals (CIs).

RESULTS

Altogether 2,127,452 children (1,092,727 boys and 1,034,725 girls) were included in our study, comprising 25,302,860 person-years. The mean time of follow-up was 11.9 years. A total of 178 children were diagnosed, with numbers of congenital malformations, particularly genitourinary abnormalities. A recent report from the Children’s Oncology Group study showed an increased risk of congenital malformations, particularly genitourinary and cardiac abnormalities (Menegaux et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005).

In general, children with congenital malformations have an increased risk of cancer (Bjørge et al, 2008). In our data, there was an increased risk of neuroblastoma in children with any congenital abnormality. A recent report from the Children’s Oncology Group study showed an increased risk of congenital malformations, particularly genitourinary and cardiac abnormalities (Menegaux et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005). Also other birth defects have been associated with the risk of neuroblastoma (Narod et al, 1997). The malformations diagnosed in the eight neuroblastoma cases in our study had the following organ system distribution: heart and blood vessels (one), lip and palate (one), digestive system (two), urinary organs (one), musculoskeletal system (two) and multiple abnormalities (one). The literature dealing with pre- and perinatal risk factors for neuroblastoma has been largely inconclusive (Hamrick et al, 2001; Narod et al, 1997).

Table 1 (Continued)

|                  | Adrenal medulla | Non-adrenal | All          |
|------------------|-----------------|-------------|-------------|
|                  | N   | RR  | (95% CI) | N   | RR  | (95% CI) | N   | RR  | (95% CI) |
| Pre-eclampsia    |     |     |          |     |     |          |     |     |          |
| No               | 80  | 1.0 | Referent | 92  | Referent | 172 | 1.0 | Referent | 24,639,244 |
| Yes              | 3   | 1.3 | (0.4 – 4.2) | 3   | 1.2 | (0.4 – 3.7) | 6   | 1.2 | (0.5 – 2.8) | 663,616 |
| Caesarean section|     |     |          |     |     |          |     |     |          |
| No               | 75  | 1.0 | Referent | 87  | 1.0 | Referent | 162 | 1.0 | Referent | 23,362,347 |
| Yes              | 8   | 1.2 | (0.6 – 2.4) | 8   | 1.0 | (0.5 – 2.1) | 16  | 1.1 | (0.6 – 1.8) | 1,940,514 |
| Paternal age (years) |     |     |          |     |     |          |     |     |          |
| <25              |     |     |          |     |     |          |     |     |          |
| 25–29            | 13  | 1.1 | (0.5 – 2.1) | 22  | 1.6 | (0.9 – 2.8) | 35  | 1.3 | (0.9 – 2.1) | 4,343,748 |
| 30–34            | 22  | 1.0 | Referent | 25  | 1.0 | Referent | 47  | 1.0 | Referent | 6,959,181 |
| 35–39            | 7   | 0.6 | (0.3 – 1.5) | 18  | 1.4 | (0.8 – 2.6) | 25  | 1.0 | (0.6 – 1.7) | 3,428,839 |
| 40+              | 5   | 0.8 | (0.3 – 2.2) | 4   | 0.6 | (0.2 – 1.7) | 9   | 0.7 | (0.3 – 1.4) | 1,886,960 |

*The total number of person-years for some variables may differ due to missing data. 4Head circumference has been recorded since 1978.

DISCUSSION

Analyses of the relations between birth and parental characteristics and the risk of neuroblastoma in a large Norwegian cohort suggested that some of these factors may have an influence. In children below the age of 18 months, there was an increased risk among those with congenital malformations and also a suggestion of increased risk when the mother had pre-eclampsia. One of the major strengths of this study is the use of large health registries, covering the total population of Norway, to get reliable data on birth and parental characteristics and cancer occurrence. Reporting of cancer cases to CRN has been compulsory since the early 1950s, and the reporting has been almost complete and of high quality (Cancer Registry of Norway, 2007). Medical Birth Registry of Norway is also based on compulsory notification of every birth or late abortion from 16 weeks of gestation onwards. Medical Birth Registry of Norway includes demographic information on the parents, the mother’s health before and during pregnancy, complications during pregnancy and delivery, length of pregnancy as well as information on the infant, including birth defects and other perinatal problems (Irgens, 2000). Within these data sources, we created a large study cohort of 2.1 million children, with a mean follow-up time of almost 12 years, to study the relations between pre- and perinatal factors and neuroblastoma. Nevertheless, only 178 cases were diagnosed, illustrating the rarity of this tumour. Although some estimates different from unity were discovered, the CIs were wide.

In general, children with congenital malformations have an increased risk of cancer (Bjørge et al, 2008). In our data, there was an increased risk of neuroblastoma in children with any congenital abnormality. A recent report from the Children’s Oncology Group study showed an increased risk of congenital malformations, particularly genitourinary and cardiac abnormalities (Menegaux et al, 2005). Similar findings were reported from the California Cancer Registry study (Urayama et al, 2005). Also other birth defects have been associated with the risk of neuroblastoma (Narod et al, 1997). The malformations diagnosed in the eight neuroblastoma cases in our study had the following organ system distribution: heart and blood vessels (one), lip and palate (one), digestive system (two), urinary organs (one), musculoskeletal system (two) and multiple abnormalities (one). The literature dealing with pre- and perinatal risk factors for neuroblastoma has been largely inconclusive (Hamrick et al, 2001; Narod et al, 1997).


| Table 2 (Continued) |
|----------------------|
| **≤ 18 months** (97 cases) | **> 18 months** (81 cases) |
| RR | (95% CI) | RR | (95% CI) |
| --- | --- | --- | --- |
| Pre-eclampsia<sup>a</sup> | No | 1.0 | Referent |
| Yes | 2.3 | (1.0 – 5.2) |
| Caesarean section | No | 1.0 | Referent |
| Yes | 1.0 | (0.6 – 2.3) | 1.0 | Referent |
| Yes | 0.9 | (0.4 – 2.1) |
| Paternal age (years) | 25–29 | 0.9 | (0.5 – 1.5) | 1.4 | (0.8 – 2.6) |
| 30–34 | 1.0 | Referent | 1.0 | Referent |
| 35–39 | 0.8 | (0.4 – 1.6) | 1.4 | (0.7 – 2.9) |
| 40+ | 0.6 | (0.2 – 1.5) | 0.9 | (0.3 – 2.5) |
| Test for trend | P = 0.4 | P = 0.1 |

<sup>a</sup>Head circumference has been recorded since 1978. <sup>b</sup>All cases were diagnosed below 18 months of age.

Schuz et al., 2001). One recent case-cohort and two relatively recent case-control studies from the US have, however, suggested that certain perinatal factors may be associated with risk. In a study from birth and cancer registries in Minnesota, a maternal history of one fetal loss, maternal drug use and small size for gestational age were associated with neuroblastoma (Johnson et al., 2008). In a study from the California Cancer Registry, associations with a number of birth characteristics were observed, including child’s race/ethnicity, gestational age/birth weight, caesarean section delivery and maternal pregnancy history (Urayama et al., 2007). In another study from the New York State Cancer Registry, pre- and post-term gestations were associated with a significant reduction in risk of neuroblastoma (Buck et al., 2001).

In mothers having pre-eclampsia during pregnancy, we found an increased risk of borderline significance in children below the age of 18 months. However, no strong associations have previously been found with diseases/conditions during pregnancy, as pre-eclampsia (Buck et al., 2001; Hamrick et al., 2001).

In summary, in a huge population-based cohort study, we found that certain birth and parental characteristics may influence the risk of neuroblastoma, but no strong associations were established.

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