Antenatal maternal bereavement and childhood cancer in the offspring: a population-based cohort study in 6 million children

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BACKGROUND: Prenatal stress may increase the susceptibility to childhood cancer by affecting immune responses and hormonal balance. We examined whether antenatal stress following maternal bereavement increased the risk of childhood cancer.

METHODS: All children born in Denmark from 1968 to 2007 (N = 2 743 560) and in Sweden from 1973 to 2006 (N = 3 400 212) were included in this study. We compared cancer risks in children born to women who lost a first-degree relative (a child, spouse, a parent, or a sibling) the year before pregnancy or during pregnancy with cancer risks in children of women who did not experience such bereavement.

RESULTS: A total of 9795 childhood cancer cases were observed during follow-up of 68 360 707 person years. Children born to women who lost a child or a spouse, but not those who lost other relatives, had an average 30% increased risk of any cancer (hazard ratio (HR) 1.30, 95% confidence interval (CI) 0.96–1.77). The HRs were the highest for non-Hodgkin disease (512 cases in total, HR 8.52, 95% CI 2.03–37.73).

CONCLUSION: Our data suggest that severe antenatal stress following maternal bereavement, especially due to loss of a child or a spouse, is associated with an increased risk of certain childhood cancers in the offspring, such as hepatic cancer and non-Hodgkin disease, but not with childhood cancer in general.

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Childhood cancer is the second leading cause of death in children in high-income countries (Parkin et al., 2002; Kaatsch, 2010). Almost half of the childhood cancers are diagnosed before 5 years of age (Kaatsch, 2010), highlighting the importance of identifying early-life risk factors (Kimmel, 2005; Anderson, 2006). Only a few risk factors have, however, been established, such as radiation for leukaemia (Giles et al., 1956; Bross and Natarajan, 1972) and cryptorchidism for testicular cancer (Garner et al., 2005), whereas associations between most other factors and childhood cancer risk remain inconclusive (Garner et al., 2005; Eden, 2010). We need to know more about the aetiology of childhood cancer to plan effective prevention strategies (Parkin et al., 2002; Kaatsch, 2010).

The fetal programming concept proposes that environmental factors operating during the periconceptional and fetal periods affect the propensity to diseases in adulthood (Gluckman and Hanson, 2006; Harris and Seckl, 2011). Maternal stress during pregnancy may cause excessive production of glucocorticoids and other hormones, which readily passes the placenta (Benediktsson et al., 1997; Gitau et al., 1998). These hormones may have immediate effects on fetal development and long-term effects on health (Kapoor et al., 2006; Davis et al., 2011; Harris and Seckl, 2011). Prenatal stress has been related to several diseases related to brain function and chronic degenerative diseases (Davis et al., 2011; Harris and Seckl, 2011). Experimental research has suggested that its effects on endocrine or immune function may also increase the susceptibility to cancer (Reiche et al., 2004; Ekbom, 2006). It remains, however, unknown whether antenatal stress can lead to childhood cancer in humans (Bermejo et al., 2007).

Bereavement by the death of a child or a husband is classified as one of the most stressful events a woman can experience (Skodol and Shrout, 1989; American Psychiatric Association, 1994; Stroebe et al., 2001). Thus, we examined whether maternal stress following bereavement before and during pregnancy increased childhood cancer risk in the offspring. We used a large population-based cohort, based on combined national data from two Nordic countries. We hypothesised that prenatal stress increased the risks of certain cancers, especially those related to the immune and endocrine functions, such as leukaemia or testicular cancer (Reiche et al., 2004; Ekbom, 2006). We further examined whether the death of a child or a spouse was associated with a higher cancer risk in offspring than the death of other relatives (Skodol and Shrout, 1989).

MATERIALS AND METHODS

This population-based cohort study used data from national registers in Denmark and Sweden, and data collection has been...
described in detail previously (Li et al, 2010). In short, all live-born children and new residents in Denmark and Sweden are assigned a unique civil personal registration number, which is used in the national registration system that includes detailed information on birth, death, and immigration. All children born in Denmark from 1968 to 2007 (N = 2743 560) and in Sweden from 1973 to 2006 (N = 3 400 212) were included and linked to their next of kin (mother, father, siblings, mother’s siblings, and mother’s parents) by using the personal number. The exposure for this study is defined as maternal bereavement by the death of a child, a spouse/partner, a parent or a sibling. The exposure time window started from 12 months before the estimated date of conception to the date of child birth, as bereavement before conception may have a long-term detrimental effect on mothers (McEwen, 1998; Gluckman et al, 2008; Harris and Seckl, 2011). Follow-up started at birth and ended at the date of a cancer diagnosis, death, emigration, 14 completed years of age (i.e., before the 15th birthday), or end of follow-up (31 December 2006 in Sweden, and 31 December 2007 in Denmark), whichever came first.

Cancer diagnosis

The Danish Cancer Registry includes data on all cancer cases in Denmark diagnosed since 1943. Quality of the Danish Cancer Registry is secured by manual coding and validation of data, which provides a high degree of completeness (Gjerstorff, 2011). From 1943 to 1977 the Registry used the modified seventh revision of the International Classification of Disease (ICD-7), and from 1978 and onwards ICD-10 was used for cancer diagnosis (Gjerstorff, 2011). The Swedish Cancer Registry was established in 1958 and contains information on all cancer cases diagnosed in Sweden since 1958, whichever came first. From 1968 to 2007 (N = 2 743 560) and in Sweden from 1973 to 2006 (N = 3 400 212) were included and linked to their next of kin (mother, father, siblings, mother’s siblings, and mother’s parents) using the personal number. The exposure for this study is defined as maternal bereavement by the death of a child, a spouse/partner, a parent or a sibling. The exposure time window started from 12 months before the estimated date of conception to the date of child birth, as bereavement before conception may have a long-term detrimental effect on mothers (McEwen, 1998; Gluckman et al, 2008; Harris and Seckl, 2011). Follow-up started at birth and ended at the date of a cancer diagnosis, death, emigration, 14 completed years of age (i.e., before the 15th birthday), or end of follow-up (31 December 2006 in Sweden, and 31 December 2007 in Denmark), whichever came first.

Table 1 Baseline characteristics of the study population

| Variables | Exposed cohort (N = 139 520) | Unexposed cohort (N = 6 004 252) |
|-----------|-----------------------------|----------------------------------|
| Sex       |                             |                                  |
| Boys      | 71 425 (51)                 | 799 073 (51)                     |
| Girls     | 68 095 (49)                 | 765 933 (49)                     |
| Age       |                             |                                  |
| <6        | 1461 (1)                    | 13 472 (1)                       |
| 6–10      | 128 399 (93)                | 1 428 407 (93)                   |
| 11–15     | 7765 (6)                    | 97 654 (6)                       |
| Gestational age |                     |                                  |
| <37 weeks | 8749 (6)                    | 91 522 (6)                       |
| ≥37 weeks | 126 326 (92)                | 1 419 911 (92)                   |
| Birth weight |                      |                                  |
| <2500 g   | 7154 (5)                    | 74 466 (5)                       |
| 2500–3250 g| 34 950 (25)                 | 398 063 (25)                     |
| ≥3251–3999 g| 68 880 (51)                | 776 834 (51)                     |
| >4000 g   | 24 830 (18)                 | 271 772 (18)                     |
| Maternal age |                    |                                  |
| ≤26       | 39 044 (28)                 | 480 211 (28)                     |
| 27–30     | 39 074 (28)                 | 450 164 (28)                     |
| >31       | 61 401 (44)                 | 634 166 (44)                     |
| Party     |                             |                                  |
| 1         | 44 965 (33)                 | 499 224 (33)                     |
| 2         | 51 789 (38)                 | 579 917 (38)                     |
| ≥3        | 39 389 (29)                 | 445 209 (29)                     |
| Maternal education |                |                                  |
| Low, ≤9 years | 65 916 (47)             | 800 766 (47)                     |
| Middle, 10–14 years | 38 258 (28) | 400 919 (28)                     |
| High, ≥15 years | 29 062 (21)        | 290 018 (21)                     |
| Maternal smoking during pregnancy |            |                                  |
| Yes       | 22 884 (19)                 | 252 803 (19)                     |
| No        | 64 821 (54)                 | 626 318 (54)                     |

*Value is n (%). Study population includes all children born in Denmark in 1968–2007, born in Sweden in 1973–2006. aData available period: 1978–2007 in Denmark, 1973–2006 in Sweden. bData available period: 1980–2007 in Denmark, 1973–2006 in Sweden. cData available period: 1991–2007 in Denmark, 1983–2006 in Sweden. dData available period: 1991–2007 in Denmark, 1983–2006 in Sweden.
who smoked during pregnancy were slightly overrepresented in the exposed cohort.

### Overall cancer risk

Table 2 presents the associations between maternal bereavement and overall childhood cancer risk in offspring. A total of 9795 children were diagnosed with cancer, of which 249 were in the exposed group. Overall, exposed children had a similar risk of cancer (hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.91–1.18), compared with unexposed children. Children born to mothers who lost an earlier born child or a spouse had a 30% elevated risk of cancer (HR 1.30, 95% CI 0.96–1.77), although the association was not statistically significant. Maternal bereavement by death of other relatives was not associated with an increased risk (HR 0.99, 95% CI 0.85–1.14). Bereavement due to unexpected death of a relative was associated with a similar HR related to bereavement due to other death. We did not observe any significant difference in HRs during the three periods within the exposure time window (12–7 months before conception, 6–0 months before conception, and pregnancy). Stratification on sex of the child yielded similar findings (data not shown).

### The risk of specific childhood cancers

Table 3 shows results for the specific childhood cancers. For most cancers, the numbers of cases were small, and differences in risk estimates between exposed and unexposed were not statistically significant. The highest risks were observed in children born to mothers who lost an earlier born child or a spouse for non-Hodgkin disease (HR 3.40, 95% CI 1.51–7.65), hepatic cancer (HR 5.51, 95% CI 1.34–22.64), and testicular cancer (HR 8.52, 95% CI 2.03–37.73).

### DISCUSSION

This large population-based cohort study revealed increased risks in children born to mothers who experienced a death of a child or spouse during pregnancy or 1 year before pregnancy for some specific childhood cancers, including non-Hodgkin disease, hepatic cancer, and testicular cancer. These excess risks were not dependent on sex of the child, birth characteristics of child (birth weight, gestational age, and Apgar score at 5 min), and maternal factors (age, parity, education, and smoking during pregnancy).

### Underlying biological mechanisms

The potential mechanisms between prenatal stress and childhood cancer remain largely unknown (Anderson et al., 2000; Reiche et al., 2004; Ekbom, 2006; Kaatsch, 2010). Excessive stress hormones (mostly glucocorticoids) in pregnant mothers could inhibit the function of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that serves as the feto-placental "barrier" to maternal hormones, which would lead to adverse effects on immune and neuroendocrine systems in the fetus (Kapoor et al., 2006; Davis et al., 2011; Harris and Seckl, 2011). Endocrine dysregulation following stress could influence fetal development and potentially programme cancer risk by neuroendocrine–immune interactions (Anderson et al., 2000; Reiche et al., 2004; Ekbom, 2006). The effects of excessive glucocorticoids on HPA axis and immune system could lead to compromised immune responses against cancer cell growth, and promote the initiation and progression of some types of cancer (Anderson et al., 2000; Reiche et al., 2004; Ekbom, 2006). It has also been suggested that such hormones, acting as growth factors, can affect stem cells, introduce malignant transformation, and increase the rate of genetic mutations (Anderson et al., 2000; Reiche et al., 2004; Ekbom, 2006).

### Overall cancer risk in offspring and antenatal maternal bereavement

We observed that prenatal stress exposure following maternal bereavement by the death of any first relative was not associated with an overall increased risk of childhood cancer. This was not unexpected because specific cancers have different aetiologies and it is unlikely that all cancers are affected by stress-induced changes (Anderson et al., 2000; Reiche et al., 2004; Ekbom, 2006). An earlier study indicated that parental death during pregnancy has been associated with an increased risk of several childhood cancers in the offspring (Bermejo et al., 2007), but these findings were based on fewer cases and the comparison group was the general population of children. We observed that the increased cancer risk in offspring was mainly restricted to maternal bereavement by the death of a child/spouse, which is consistent with our prior hypothesis regarding severity of stress (Skodol and Shrou, 1989). The relative risks in relation to different periods within the exposure time window were similar, possibly due to the variances in the sensitive timing windows for different individual cancers (Anderson et al., 2000; Reiche et al., 2004).

Other prenatal factors, such as birth weight or birth order, have been shown to be associated with childhood cancer (Tower and Spector, 2007; Von Behren et al., 2011). Various possible biological

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**Table 2** HRs for childhood cancer according to exposure (bereavement) status

| Bereavement                    | Cancer cases (rate, 1/1000) | Crude HR | Adjusted HR (95% CI)* | Adjusted HR (95% CI)ᵇ |
|-------------------------------|-----------------------------|----------|------------------------|------------------------|
| All exposed                   | 249 (1.8)                   | 1.12     | 1.04 (0.91–1.18)       | 1.04 (0.91–1.18)       |
| Type of the deceased relative |                             |          |                        |                        |
| Child/spouse                  | 48 (2.2)                    | 1.29     | 1.30 (0.96–1.75)       | 1.30 (0.96–1.77)       |
| Other relatives               | 201 (1.7)                   | 1.09     | 0.99 (0.86–1.15)       | 0.99 (0.85–1.14)       |
| Cause of death                |                             |          |                        |                        |
| Unexpected death              | 30 (1.9)                    | 1.16     | 1.14 (0.79–1.64)       | 1.16 (0.81–1.67)       |
| Other death                   | 219 (1.8)                   | 1.12     | 1.03 (0.89–1.18)       | 1.02 (0.89–1.18)       |
| Timing of death               | 249 (1.8)                   | 1.12     | 1.04 (0.91–1.18)       | 1.04 (0.91–1.18)       |
| 12–7 Months before conception | 78 (2.0)                    | 1.20     | 1.10 (0.87–1.39)       | 1.11 (0.87–1.40)       |
| 6–0 Months before conception  | 81 (1.8)                    | 1.15     | 1.05 (0.83–1.32)       | 1.06 (0.84–1.33)       |
| Pregnancy                     | 90 (1.6)                    | 1.04     | 0.98 (0.80–1.22)       | 0.96 (0.77–1.19)       |
| Unexposed                     | 9546 (1.6)                  | 1.0 (ref)| 1.0 (ref)              | 1.0 (ref)              |

Abbreviations: CI = confidence interval; HR = hazard ratio. *Adjusted for country, sex, maternal factors at child birth (age, education, smoking during pregnancy). ‡Adjusted for country, sex, maternal factors at child birth (age, parity, education, and smoking during pregnancy); birth characteristics (low birth weight, Apgar score at 5 min, gestational age), restricted to period when birth characteristics were available (1978–2007 in Denmark, 1973–2006 in Sweden).
mechanisms have been proposed, including the involvement of insulin growth factors or maternal oestrogen (Milne et al, 2007; Tower and Spector, 2007; Von Behren et al, 2011), which have also been related to prenatal stress (Wadhwa, 2005). As the estimates did not change when we adjusted for these factors, the association between maternal stress exposure and childhood cancer risk in offspring may operate via other pathways (Petridou et al, 1990; Greaves, 2002; Law, 2008).

### Risk of specific childhood cancers in offspring and antenatal maternal bereavement

The associations between prenatal stress following maternal bereavement and risk of some main childhood cancers are noteworthy. So far, studies on fetal origins of childhood cancer have mostly focused on the associations between leukaemia and certain environmental exposures (Linet et al, 2003; Little, 2009). We observed an increased risk of leukaemia (albeit not statistical significant) and non-Hodgkin’s lymphoma as also shown in another study (Bermejo et al, 2007). Our findings also support a role of prenatal stress for testicular cancer (Bermejo et al, 2007), consistent with observations on cryptorchidism (Schottenfeld et al, 1980), indicating a role of intrauterine hormonal disturbances (Garner et al, 2005). Although low birth weight (Reynolds et al, 2004), maternal age, and smoking during pregnancy have been proposed to be associated with hepatoblastoma (McLaughlin et al, 2006), the associations are weak and the aetiology of hepatoblastoma remains unclear. Stress hormones, acting as growth factors, might have a role in the pathways (Ekblom, 2006).

### Strengths and limitations

The strengths of our study include the longitudinal design, large sample size, almost complete follow-up, and detailed data on covariates (Frank, 2000). To evaluate the hypothesis of an association between prenatal stress exposure and offspring risk of childhood cancer is difficult due to the rarity of childhood cancer and difficulties in measuring stress exposure. Much of the heterogeneity of previous results might be due to small sample sizes and lack of control for potential confounding by both child and maternal factors. The population-based cohort design based on high-quality data met the above challenges. The design also eliminates the impact of selection and recall bias, which are common problems in case-control studies. The registry system in the Nordic countries provides both a complete case ascertainment and accurate linkage with other data, which allow complete follow-up with least impact of misclassification error (Frank, 2000; Gjerstorff, 2011).

One limitation is that we lack information on risk factors after birth. We cannot rule out the role of other factors related to bereavement, such as breast feeding and other environmental exposures in later life. Although our cohort is very large, the small numbers of specific cancer cases limited the study power investigating the associations between bereavement and risks of many specific cancer types. Thus, both positive and negative findings should be read with caution as indicated by the wide CIs for the estimates. Another limitation of the study is that we only included exposure to stress due to loss of a close relative, not stress from other sources. Stress could arise from many other situations, such as the death of a close friend, or a serious illness of a next to kin, which may have a similar effect, which will be misclassified as non-exposed in this study. This misclassification is likely non-differential and would thus have drawn the risk estimates towards unity.

### CONCLUSIONS

Severe antenatal stress exposure due to maternal loss of the closest family member, a child or a spouse, was associated with an
increased risk of certain childhood cancers in offspring, but not with the childhood cancer in general. Hormonal disturbance may be involved in the observed associations (Reiche et al., 2004; Eknbom, 2006), but our findings may be due to chance and need to be replicated in an independent data source.

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Conflict of interest

The authors declare no conflict of interest.

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