Molar pregnancy and childhood cancer: a population-based linkage study from Denmark

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We observed a relative risk of 1.40 (95% confidence interval: 0.86–2.16) for cancers diagnosed under the age 20 in 6192 offspring of 3431 mothers with a molar pregnancy, indicating it is not a major determinant of childhood cancer.

MATERIALS AND METHODS

Women who had a molar pregnancy before 2005 were identified using the Danish National Hospital Register, which contains information for virtually all non-psychiatric hospital admissions in Denmark since 1977. Details of children born to these women were obtained from the National Central Population Register (CPR), which was established in 1968 with all citizens having unique personal identification numbers that permit linkage between registers. The follow-up for cancer incidence, determined by linking to the National Danish Cancer Registry which has been in operation since 1943 (Storm et al, 1997), was up to 31 December 2003, the most recent year with complete registration. Although there were no age restrictions for the linkage, we decided to exclude only cancers diagnosed before the age of 20 years in the analyses.

In our analysis, the number of observed cases was compared with those expected. Expected numbers were determined by multiplying the number of person-years of cohort members by the incidence rates of primary cancer in the general population of Denmark (excluding non-melanoma skin cancer), in sex-specific 5-year age groups and 5-year calendar periods of observation. Standardised incidence ratios (SIRs) were calculated by dividing the observed and expected numbers, and exact 95% confidence limits of the SIRs obtained on the assumption of a Poisson’s distribution of the observed cancers (Breslow and Day, 1987). Additional analyses involved restricting the age of follow-up to 14 years and to children born after their mother’s molar pregnancy, the latter being primarily for comparison with previously published data (Roman et al, 2006). Data were also stratified by sex.

RESULTS

Approximately 1 million women gave birth between 1977 and 2005 from which 3431 women with at least one molar pregnancy were identified. In total, 7403 children were born to these women, 507 of which were excluded as they were born after 31 December 2003, the cut-off for linking to the cancer registry. The final cohort of 6896 children was followed up for cancer diagnosis until they were 20 years old or 31 December 2003, whichever came first, accruing 83 945 person-years under risk. Characteristics of the 20 children who were diagnosed with cancer within this period of time are shown in Table 1. Non-melanoma skin cancers were excluded (one case).

The overall SIR based on 20 observed cases vs 14.3 expected was 1.40 (Table 2). When the data were stratified by cancer type no substantial differences were observed; based on two cases, the SIR was highest for testicular cancer. Furthermore, there were no apparent differences between boys (SIR 1.49) or girls (SIR 1.28). When we restricted the age of diagnosis from 0 to 14 years of age, we observed an overall SIR of 1.10 (95% confidence interval (CI); 0.58–1.88). To compare our data directly with that previously published (Roman et al, 2006), we examined cancer risk in children aged 0–14 years old whose mothers had had a previous molar pregnancy. We observed SIRs of 0.87 (95% CI: 0.28–2.03; 5 observed/5.8 expected), 1.77 (95% CI: 0.48–4.53; 4/2.3), and 0.00
was sufficient statistical power in the study to detect a twofold risk increase.

Children born after 1977 but whose mothers had had their only molar pregnancy before this time were not covered in the cohort but were included in the calculation of the reference rates. However, since molar pregnancy is a rare event, the number of such children is a very small proportion of all cancer cases and therefore the misclassification results in a minor loss of statistical power rather than a bias in the risk estimation. In contrast to the UKCCS analyses (Roman et al, 2006) our age range was 0–19 years and children were included irrespective of whether their mother’s molar pregnancy was before or after the pregnancy with the index child – the design of the UK study meant obstetric data were only available for reproductive events before the birth of the index child. We did, however, generate risk estimates according to the UK analytical model for direct comparison.

The association between molar pregnancy and childhood cancer raises the interesting possibility of a common aetiology. Indeed, Roman et al (2006) speculated about the potential involvement of epigenetic mechanisms in relation to both molar pregnancy and childhood cancer development. Both childhood cancer and hydatidiform mole (HMs) are rare conditions with around 1 in 600 children likely to develop cancer before they are 15 years old (Parkin et al, 1998) and HM likely to occur in 1 in 1500 pregnancies in the western world (Altieri et al, 2003). Hydatidiform moles generally arise from an abnormal fertilisation and have been associated with the de-regulation of imprinted genes (Altieri et al, 2003; Slim and Mehio, 2007). Thus, while epigenetics is not a new concept with respect to the pathogenesis of HM (Kaji and Ohama, 1977), for childhood cancer it is a relatively new and expanding area of research. Loss of imprinting has been implicated in a number of congenital syndromes, some of which, such as Beckwith–Wiedemann syndrome, predispose towards certain childhood cancers (DeBaun and Tucker, 1998). The observation that childhood cancer can in some cases originate in utero, combined with the knowledge that many imprinted genes have key functions in regulating embryonic development (Robertson, 2005) suggests that it may be similar or even the same epigenetic predisposition that gives rise to both these conditions.

Recent work has identified NALP7, part of the CATERPILLAR family of proteins that are involved in cellular inflammatory responses to infectious processes, as the gene causing familial recurrent HMs (Tschopp et al, 2003; Murdoch et al, 2006). While its exact role in familial recurrent HMs are unknown, for example it has no established role in DNA methylation, there have been several possible biological mechanisms put forward (Slim and Mehio, 2007). The most interesting of these in relation to childhood cancer, in particular childhood leukaemia, is the involvement of NALP7 in the cellular immune response. An abnormal immune relationship between a mother and a fetus has been associated with irregular pregnancy outcomes such as HM and choriocarcinoma (reviewed by Slim and Mehio, 2007). Thus insight into the aetiology of some childhood cancers may be gained by investigating the immune function and response of mothers of children with such conditions.

Importantly from a public health perspective the lack of a strong association between molar pregnancy and cancer in children and teenagers confirms the fact that molar pregnancy is not a major determinant of cancer in the young. However, the issue of overlapping aetiology remains one to be investigated in future research.

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