Childhood and Adult Cancer in Twins: Evidence from the Utah Genealogy

Rachel E. Neale,1,2 Geraldine Mineau,3 David C. Whiteman,1 Pat A. Brownbill,2 and Michael F.G. Murphy2

1Queensland Institute of Medical Research, Brisbane, Australia; 2Childhood Cancer Research Group, Oxford, United Kingdom; 3Huntsman Cancer Institute and Department of Oncological Sciences, University of Utah, Salt Lake City, Utah

Abstract

Objective: Evidence suggests that the in utero environment may contribute to subsequent development of cancers in childhood and adulthood. Raised levels of estrogen during pregnancy may be the primary in utero etiologic factor. Mothers of twins have higher estrogen levels during pregnancy than mothers of singletons, therefore, assessment of cancer risk in twins may be informative.

Method: We conducted a retrospective cohort study of cancer among twin and singleton newborns selected from the Utah Population Database, matched on birth year and sex. Cancer diagnoses were determined by linkage with the Utah state cancer register. Relative rates of all cancers in childhood and in adulthood in twins compared with singletons, and for specific cancers including testicular, breast, and melanoma, were calculated using Poisson regression.

Results: Twin (35,271) and singleton (74,199) births were identified, among whom there were 336 and 691 cancer diagnoses, respectively. The relative risk (RR) of childhood cancer in twins compared with singletons was 0.82 [95% confidence interval (CI) 0.55-1.24] and of adult cancer was 1.06 (0.92-1.22). We found nonsignificant increases in risk among adult twins for cancers of the breast, prostate, tests, lymphatic system, thyroid, and large bowel. The largest departures from unity were for testicular cancer (RR 1.47; 95% CI, 0.73-2.95) and melanoma (RR 0.67; 95% CI, 0.42-1.06).

Conclusions: These results are consistent with the body of evidence suggesting that twins have a reduced risk of cancer in childhood. Although there is no overall differential in adult cancer risk, these data support the hypothesis that the in utero environment may play an important role in specific cancers. (Cancer Epidemiol Biomarkers Prev 2005;14(5): 1236–40)

Introduction

There has been increasing interest in the hypothesis that in utero environment of the developing fetus may influence the subsequent development of cancers in both childhood and adulthood. For example, it is speculated that raised levels of estrogen during pregnancy may be a primary in utero etiologic factor, particularly for hormone-dependent cancers such as those of the breast or testis.

Given that prospective studies of maternal estrogen levels and subsequent risk of cancer in the offspring are not generally feasible, surrogate markers of unusual intrauterine hormonal environments have been employed in their stead. Mothers of twins have higher circulating levels of estrogen and other hormones during pregnancy than those carrying singleton babies (1), hence comparison of cancer rates between twins and singletons may be informative. Twins may be at higher risk of some cancers because of in utero exposure to higher levels of circulating pregnancy hormones. On the other hand, twins may have lower risks of other cancers due to their generally lower birth weight (2).

To date, most studies of the association between twinning and childhood cancer have found a small decrease in risk, but no individual study has been large enough to preclude the possibility that the protective effect observed was a chance finding. However, a recent metaanalysis of the six published prospective studies suggested that the observation may be real (3). It is not known whether the effect extends to both the main classes (solid and hematopoietic) of childhood tumor, although the data suggest this.

There have been several studies of cancer risk in adult twins, both of overall cancer risk (4-7) and of specific cancers (8-11), but the results to date have not been consistent. We have therefore studied a moderately large and unselected cohort of twins to confirm the protection afforded against childhood cancer, with further investigation of solid and hematopoietic tumors, and to further investigate tumor occurrence in adult twins.

Materials and Methods

Data Sources. We conducted a retrospective cohort study of cancer occurring in childhood and adulthood among matched cohorts of twin and singleton newborns. Subjects were selected from the Utah Population Database, a computerized database containing over seven million records comprised of multiple linked data sets including genealogy, births and deaths, and cancer registers. The genealogy records were computerized in the mid to late 1970s (12, 13) and are annually linked to other Utah population data sets. Demographic studies have verified the quality of the data (14). This population is biologically representative of a broad spectrum of the White U.S. population and is genetically similar to other Northern European–derived populations. The population has a low inbreeding rate that is very similar to that of the U.S. population due to a large founding population and high rates of immigration from a diverse group of outside populations (15, 16). This study was...
approved by the Utah Resource for Genetic and Epidemiologic Research, which administers access to the Utah Population Database (17) and the Bancroft Centre Human Research Ethics Committee.

**Study Participants.** All children from multiple births born in Utah between January 1, 1934 and December 31, 2000 (hereafter referred to as twins) and registered in the Utah Population Database were eligible for analysis. From the same population register, we selected a comparison cohort of singleton children, matched in a 2:1 ratio to each twin child on birth year and sex.

We restricted the analysis to liveborn offspring of multiple and singleton pregnancies, although stillbirth of one twin did not result in exclusion of its co-twin from the cohort. Similarly, we excluded a small number of singleton children who were stillborn, thus after their exclusion, some twins were matched to only one singleton.

**Data Abstraction.** Information extracted from the linked data included the birth date, birth weight, multiplicity, birth order, and date of death. We used records from the Utah Cancer Registry and Utah death certificates to ascertain diagnoses of cancer. Utah did not have a statewide cancer registry until 1966, so only incident cancers recorded between January 1966 and December 2001 were included in the analysis. We elected not to use deaths from cancer as a marker of incident cancers prior to 1966.

**Statistical Analysis.** Poisson regression was used to compare the incidence rate ratio for twins relative to singletons, after adjustment for date of birth, attained age at time of exit from the study, birth order and (log) duration of risk exposure. Risk exposure was calculated as the number of days from the date the subject was 1 week old (or else January 1, 1966 if the child was born prior to 1966) until the lower of the date of cancer diagnosis, or if no cancer occurred, the date of censoring (the date of death or December 31, 2001 if still alive). Cancers were subsequently stratified into those occurring in childhood (prior to age 15) and those occurring in adulthood (aged 15 or over). For the analysis of childhood cancer, surviving children were censored at the date of their 15th birthday. For the analysis of cancers in adulthood, subjects who developed cancer in childhood were excluded, and risk exposure was calculated from the date of the subject’s 15th birthday. Secondary analyses were done to estimate site-specific cancer rate ratios (breast, cervix, prostate, leukemia, testis, melanoma, colorectal, lymphoid, and brain). These were selected on the basis that previous data have suggested either that there may be an association with twinning or that the tumor may have a hormonal etiology. All Poisson regressions models were done using PROC GENMOD in SAS v 8.2 (Cary, NC).

The zygosity of the twins was not available on the Utah Population Database. We therefore stratified the analysis by like- versus unlike-sex twins, only including the relevant matched singletons in each case.

**Results**

There were 37,141 liveborn children from multiple births identified between January 1, 1934 and December 31, 2000. Children who died prior to January 1, 1966 (n = 947) or were born later than January 1, 1966 but who survived less than 1 week (n = 923) were subsequently excluded, leaving 35,271 children who were included in the analysis. This consisted of 34,334 twins and 937 children from higher order births.

Of 74,282 eligible singleton births in the matched cohort, 83 were stillborn, 484 died prior to 1966 and 221 born thereafter died within the first week after birth, leaving 73,494 singleton children meeting the inclusion criteria.

Among twins who survived for at least 1 week, 753 (2.1%) died during the follow-up period, compared with 1,142 singletons (1.6%). Forty-one percent of twin deaths occurred at less than 1 year of age and another 12% during childhood, compared with 8% and 15%, respectively, among singletons.

The median follow-up time in twins was 19 years (IQ range 15-34) and in singleton children it was 20 years (IQ range 9-35 years). The maximum age at the end of follow-up was 68 years in both twin and singleton cohorts. Approximately 60% of the twin and singleton cohorts had follow-up time in adulthood and 90% in childhood.

Cancer was diagnosed in 336 twins, of whom 33 (10%) were diagnosed in childhood. In comparison, 691 singletons developed cancer, of whom 81 (12%) were diagnosed in childhood. Eleven sets of twins were concordant for cancer; in six of these families, the cancers were of the same type and were diagnosed less than 5 years apart (two sets of twins had prostate cancer, one colon, one breast, one cervix, and one thyroid).

We separately analyzed the matched cohorts according to the sex combination of the multiple birth offspring. We excluded the small number of twins for which the sex of at least one member of the twin pair was not known (n = 700). Among the subcohort of 23,944 like-sex twins or higher order births there were 217 cancers occurring in twins (21 in childhood), whereas in the subcohort of their eligible matched singletons (n = 48,637), there were 443 diagnoses of cancer (55 occurring in childhood). Among the subcohort of unlike-sex twins (n = 10,627) there were 114 cancers in twins (12 in childhood), whereas among the subcohort of 21,440 matched singletons, there were 179 cancer diagnoses (26 in childhood).

**Twin Membership and Cancer.** Overall, we found no difference in the risk of cancer between twins and singletons and this null finding held for analyses of cancers occurring only in adulthood (Table 1). Twins seemed to have a slightly lower risk of cancer in childhood, although this finding was not statistically significant [relative risk (RR), 0.82; 95% confidence interval (CI), 0.55-1.24]. The nonsignificantly reduced risk of childhood cancer was observed both for like-sex and unlike sex twins. There was no association between twinning and adult cancer risk among like-sex twins, but among unlike-sex twins there was a significantly increased risk of all adult cancer (RR, 1.36; 95% CI, 1.05-1.76).

Analyses of associations between twinning and specific cancers were hampered by small numbers (Table 2). We found nonsignificantly increased relative risks among twins for cancers of the breast, prostate, testis, lymphatic system, thyroid, and large bowel. The largest deviations from unity were observed for relative risks of testicular cancer (RR, 1.49; 95% CI, 0.74-3.01) and melanoma (RR, 0.68; 95% CI, 0.43-1.08). The negative association with childhood tumors seemed to be restricted to solid tumors, although confidence intervals were wide and overlapping between hematopoietic and solid tumors.

**Discussion**

In this population-based cohort study, we found a small reduction in the risk of cancers occurring during childhood among twins. Like all previous studies investigating this rare exposure (multiple birth) and rare outcome (childhood cancer), our results were not statistically significant. However, they contribute to the worldwide data set and are entirely consistent with a pooled estimate of all previous cohort studies in which reduced total childhood cancer risk was reported (3). Our findings of reduced risks among twins for solid tumors of childhood, but not for leukemias, is at odds with other results in which no such distinction was found (18-20), but given the wide confidence intervals, this may well be a chance finding.
Table 1. Associations between twin births and total cancer cases in childhood and adulthood

<table>
<thead>
<tr>
<th>Number of cancers</th>
<th>All twins</th>
<th>Like-sex twins</th>
<th>Unlike-sex twins</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twin</td>
<td>Singleton</td>
<td>Twin</td>
<td>Singleton</td>
</tr>
<tr>
<td>All cancers</td>
<td>140</td>
<td>276</td>
<td>105</td>
<td>1.15 (0.94-1.42)</td>
</tr>
<tr>
<td>Males</td>
<td>20</td>
<td>38</td>
<td>13</td>
<td>1.10 (0.64-1.91)</td>
</tr>
<tr>
<td>Females</td>
<td>196</td>
<td>415</td>
<td>112</td>
<td>0.58 (0.31-1.09)</td>
</tr>
<tr>
<td>Total</td>
<td>336</td>
<td>691</td>
<td>217</td>
<td>1.06 (0.92-1.21)</td>
</tr>
<tr>
<td>Childhood cancer</td>
<td>17</td>
<td>54</td>
<td>11</td>
<td>1.15 (0.92-1.45)</td>
</tr>
<tr>
<td>Males</td>
<td>13</td>
<td>43</td>
<td>8</td>
<td>0.82 (0.55-1.24)</td>
</tr>
<tr>
<td>Females</td>
<td>33</td>
<td>81</td>
<td>21</td>
<td>0.55 (0.25-1.21)</td>
</tr>
<tr>
<td>Adult cancer</td>
<td>120</td>
<td>238</td>
<td>82</td>
<td>1.15 (0.92-1.45)</td>
</tr>
<tr>
<td>Males</td>
<td>183</td>
<td>372</td>
<td>114</td>
<td>1.15 (0.92-1.45)</td>
</tr>
<tr>
<td>Females</td>
<td>303</td>
<td>610</td>
<td>196</td>
<td>1.06 (0.92-1.22)</td>
</tr>
</tbody>
</table>

*Adjusted for birth date and parity and age at exit from the study.

The results generated in this population-based study are unlikely to be due to inherent bias. The two cohorts were sampled from the same population register at the same time, so differential ascertainment of participants is unlikely. Similarly, follow-up of both cohorts was through the same set of linked population databases which have high coverage. Among those who were born prior to 1986 and were therefore old enough to have attained the age when they might obtain a drivers license or marry, we undertook further linkage within the Utah Population Database to assess similarity of follow-up between the twin and singleton cohorts. Seventy-one percent of the twin cohort and 72% of the singleton cohort born prior to 1986 had at least one follow-up record (death certificate, cancer record, marriage certificate, drivers license, or registered as a parent on a birth certificate) with the proportion of each not differing significantly between the two cohorts. Thus, there is no evidence of differential follow-up of the two cohorts. Our study did however experience several other limitations. Firstly, the study had insufficient power to detect associations with specific cancer types, although this challenge is faced by all those investigating causal links between rare exposures and rare outcomes. These data are nonetheless valuable, as they add to the literature and can be combined with other data sets. Secondly, we were unable to analyze differences between monozygotic and dizygotic twins except by sex combination, which again limits the power to investigate associations. Finally, we did not adjust for parental age, which is associated with both twinning (21) and possibly with certain types of cancer in childhood (22), although not with cancer in adulthood to our knowledge. However, any resulting bias would have attenuated the protective effect of twinning seen in this study, and adjustment for parity will have resulted in considerable adjustment for maternal age.

Table 2. Associations between twinning and specific cancer types

<table>
<thead>
<tr>
<th>Number of cancers</th>
<th>All twins</th>
<th>Like-sex twins</th>
<th>Unlike-sex twins</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twin</td>
<td>Singleton</td>
<td>Twin</td>
<td>Singleton</td>
</tr>
<tr>
<td>Breast</td>
<td>54</td>
<td>95</td>
<td>39</td>
<td>1.19 (0.85-1.68)</td>
</tr>
<tr>
<td>Cervix</td>
<td>39</td>
<td>92</td>
<td>22</td>
<td>0.86 (0.59-1.27)</td>
</tr>
<tr>
<td>Prostate</td>
<td>22</td>
<td>35</td>
<td>17</td>
<td>1.30 (0.74-2.26)</td>
</tr>
<tr>
<td>Testis</td>
<td>14</td>
<td>19</td>
<td>8</td>
<td>1.47 (0.72-2.99)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>24</td>
<td>87</td>
<td>14</td>
<td>0.67 (0.42-1.06)</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>25</td>
<td>46</td>
<td>17</td>
<td>1.27 (0.77-2.09)</td>
</tr>
<tr>
<td>Brain</td>
<td>10</td>
<td>29</td>
<td>8</td>
<td>0.74 (0.36-1.54)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>21</td>
<td>40</td>
<td>16</td>
<td>1.19 (0.69-2.04)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>20</td>
<td>41</td>
<td>11</td>
<td>1.08 (0.63-1.86)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>22</td>
<td>36</td>
<td>12</td>
<td>1.29 (0.75-2.24)</td>
</tr>
<tr>
<td>Hematopoietic in childhood</td>
<td>16</td>
<td>27</td>
<td>10</td>
<td>1.14 (0.61-2.13)</td>
</tr>
<tr>
<td>Solid tumors in childhood</td>
<td>17</td>
<td>54</td>
<td>11</td>
<td>0.65 (0.38-1.13)</td>
</tr>
</tbody>
</table>

*Adjusted for birth date and parity.
were required to be alive at the date of diagnosis of the cancer. The generally lower birth weight of twins has also been invoked as an explanation for their reduced risk of childhood cancer (3). Recent metaanalysis of birth weight and leukemia in children found that babies with higher birth weight were at significantly higher risk of developing childhood leukemia (2). However, this same association does not seem to be apparent for the diverse group of solid tumors when grouped (23, 24), but high birth weight may increase the risk of specific tumor types (25-28). Assuming the association between high birth weight and childhood cancer is real, then possible underlying mechanisms might include variation in circulating levels of insulin-like growth factor-I or simply in the absolute number of cells in which a genetic aberration could occur (29).

We were unable to fully explore the effect of birth weight in this study due to a high proportion of missing values. Among those for whom birth weight was available, we found no association with risk of childhood or adult cancer, and adjusting for birth weight in the subcohort for whom it was available did not alter the estimates of risk presented (data not shown). We found some nonsignificant evidence that twins born second may have a higher risk of developing childhood cancer (RR, 1.65; 95% CI, 0.78-3.49) but adjusting for birth order within the twin pair did not alter the overall estimates of risk.

We found, as have several others (4, 6, 7), that there is no overall risk in risk of adult cancer among twins, although not all studies are in agreement, with some finding a small reduction in overall risk of adult cancer among twins, although some did not (41-44). Aside from chance, the most likely explanation intuitively is that twins have reduced opportunity for sun exposure in childhood compared with children from singleton births, related to family size and socioeconomic status (45). Unfortunately, although we could adjust for birth order, we were unable to adjust or stratify for family size, which would help to distinguish between this and a possible hormonal etiology. The possibility that in utero exposures may contribute to melanoma susceptibility merits further investigation in related data sets.

In summary, these results support hypotheses that in utero exposures may be important for childhood cancer, and for breast and testicular cancers and possibly melanoma in adulthood.

Acknowledgments

We would like to acknowledge the technical support of Carole Schaefer in extraction of data from the Utah Population Database. Tim Bishop was instrumental in designing studies based on the Utah Population Database.

References

Cancer Epidemiology, Biomarkers & Prevention

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