Pregnancy Outcomes among Adult Survivors of Childhood Cancer in the British Childhood Cancer Survivor Study

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Abstract

Purpose: We used data from the first large-scale overwhelmingly population-based study (a) to quantify the risk of adverse pregnancy outcomes in survivors of childhood cancer in relation to cancer type and treatment and (b) to assess live birth rates relative to the general population.

Methods: A questionnaire, including questions inquiring about pregnancy outcomes, was completed by 10,483 survivors. A total of 7,300 pregnancies were reported. Odds ratios (OR) for live birth, miscarriage, termination, stillbirth, premature birth, and low birth weight were calculated for different types of childhood cancer and by whether initial treatment involved chemotherapy and abdominal or brain irradiation. For females, the observed number of live births was compared with that expected based on the general population of England and Wales.

Results: Female survivors exposed to abdominal irradiation had a significantly increased OR of delivering preterm [OR, 3.2; 95% confidence interval (95% CI), 2.1-4.7] and producing offspring with a low birth weight (OR, 1.9; 95% CI, 1.1-3.2). An increased OR of miscarriage was also associated with abdominal radiotherapy (OR, 1.4; 95% CI, 1.0-1.9). The number of live births observed from all female survivors was two thirds of that expected (O/E, 0.64; 95% CI, 0.62-0.66) and lowest among survivors treated with brain (O/E, 0.52; 95% CI, 0.48-0.56) and abdominal radiotherapy (O/E, 0.55; 95% CI, 0.50-0.61).

Conclusion: Female survivors of childhood cancer treated with abdominal radiotherapy are at 3-fold increased risk of delivering preterm, 2-fold increased risk of low birth weight, and a small increased risk of miscarriage. Overall, female survivors produce considerably fewer offspring than expected, particularly those treated with abdominal or brain radiotherapy. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2239-47)

Introduction

Given the major improvements in the treatment of childhood cancer over the last 4 decades, a large number of children treated for cancer have survived into adulthood. Although some survivors became infertile as a result of treatment with high-dose irradiation or cytotoxic chemotherapy (1-4), many survivors remain fertile and wish to have children. One of the concerns childhood cancer survivors express is that treatment may adversely affect reproductive function and increase the risk of adverse pregnancy outcomes (5).

Previous studies have shown that radiotherapy to the pelvic area increases the risk of low birth weight and premature birth in the offspring of women who have survived childhood cancer (6-9) primarily among survivors of Wilms' tumor (10-13). Furthermore, there is some evidence that the risk of miscarriage among women exposed to abdominal irradiation is also increased (7, 9, 14). Exposure to brain irradiation was associated with a slightly increased risk of miscarriage among women in two previous studies (7, 14).

Despite the above observations, one of the principal uncertainties in predicting the risk of adverse pregnancy outcomes arises from the fact that most previous studies lacked sufficient statistical power or were not population based, which may have hindered accurate or valid quantification of risks. Therefore, the main objective of this study was to quantify the risk of adverse pregnancy outcomes among both female survivors and partners of male survivors of childhood cancer in relation to aspects of childhood cancer and its treatment within the first large-scale population-based cohort on this topic. A secondary objective was to assess live birth rates of female survivors of childhood cancer compared with the general population.

Materials and Methods

British Childhood Cancer Survivor Study. We used data from the British Childhood Cancer Survivor Study

Drugbank does not contain any related drug information for this article.
BCCSS), a large-scale cohort study that examines the late effects of treatment among survivors of childhood cancer who were diagnosed with childhood cancer between 1940 and 1991, in Britain, and had survived for at least 5 y (15). The cohort was ascertained through the National Registry of Childhood Tumours, which is maintained by the Childhood Cancer Research Group (CCRG) at the University of Oxford. The National Registry of Childhood Tumours is population based since 1962, and before then, a special attempt was made to locate all treatment centers for which records were available indicating that a complete series of patients could be ascertained. The proportion of 5-y survivors diagnosed before 1962 included in the BCCSS is <7%.

Information on type of childhood cancer, site of tumor, initial treatment, and demographics was provided by CCRG. As part of the BCCSS, a questionnaire ascertaining adverse health outcomes was sent to those survivors who were at least 16 y of age and contactable through their general practitioner (n = 13,211). In total, 10,483 of the 14,836 survivors who were alive and ages at least 16 y at the time completed a questionnaire yielding a response rate of 71% (15). The questionnaire can be downloaded online.5

Adverse pregnancy outcomes assessed in the questionnaire and evaluated in this investigation included miscarriage, stillbirth, termination, premature birth, and low birth weight. A pregnancy ending before gestational week 24 without the fetus surviving was considered a miscarriage (i.e., spontaneous abortion). Stillbirths were defined as pregnancies ending with the death of the fetus in gestational week 24 or later (16). Medically induced abortions were referred to as terminations. Live births occurring before 37 wk of gestation were considered premature. Low birth weight was defined as a live birth weighing <2,500 g. Pregnancies were excluded from analysis if the pregnancy was of multiple birth, occurred before the onset of the cancer, or was achieved by assisted reproductive technology or if the outcome was unknown.

Information on initial treatment had been obtained by CCRG in a dichotomous format [radiotherapy (yes/no); chemotherapy (yes/no)] by visiting relevant hospitals and abstracting clinical records. Information on the site of the childhood tumor and whether the initial treatment included radiotherapy was used to classify survivors into four mutually exclusive categories: no radiotherapy, radiotherapy other than to the brain or abdomen, radiotherapy to the brain, and radiotherapy to the abdomen. Survivors who were treated with radiation for a brain tumor, retinoblastoma, or nasopharyngeal tumor or who received prophylactic radiotherapy for leukaemia were classified as having received brain irradiation. Radiotherapy to the abdomen was defined as any irradiated tumor below the diaphragm and above the knees. Survivors for whom treatment data were missing were excluded from analyses.

Statistical Analysis. Logistic regression models were used to calculate odds ratios (OR) of the various adverse pregnancy outcomes by type of childhood cancer, treatment with chemotherapy, treatment with brain radiotherapy, abdominal radiotherapy, or other radiotherapy. ORs were also calculated for Wilms' tumor survivors treated with abdominal irradiation, as Wilms' tumor survivors would have received among some of the highest doses of abdominal irradiation and also compromise a sufficiently large group to fully consider separately.

Each specific natural pregnancy outcome was evaluated relative to all natural pregnancy outcomes, specifically live births, miscarriages, and stillbirths. Terminations

Figure 1. Flowchart of pregnancy outcomes for female and male survivors.
Table 1. ORs of pregnancy outcomes among female survivors of childhood cancer

<table>
<thead>
<tr>
<th>Natural pregnancy outcome*</th>
<th>Termination (n = 485)**</th>
<th>Low birth weight (n = 262)**</th>
<th>Premature (n = 368)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Live birth (n = 2,998)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriage (n = 607)</td>
<td>132 (16.7%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stillbirth (n = 23)§</td>
<td>5 (0.6%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Termination (n = 485)†</td>
<td>5 (13.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abnormal birth (n = 70)‰</td>
<td>33 (6.2%)</td>
<td>1</td>
<td>62 (12.9%)</td>
</tr>
<tr>
<td>Type of childhood cancer ¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia (reference)</td>
<td>549 (69.4%)</td>
<td>1</td>
<td>132 (16.7%)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>251 (72.5%)</td>
<td>1.2 (0.8-1.8)</td>
<td>49 (14.2%)</td>
</tr>
<tr>
<td>NHL</td>
<td>156 (74.6%)</td>
<td>1.4 (0.9-2.4)</td>
<td>28 (13.4%)</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>577 (77.0%)</td>
<td>1.5 (1.0-2.1)</td>
<td>90 (12.0%)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>139 (73.5%)</td>
<td>1.5 (0.8-2.3)</td>
<td>29 (15.3%)</td>
</tr>
<tr>
<td>NHL-retinoblastoma</td>
<td>213 (77.7%)</td>
<td>1.5 (0.7-2.3)</td>
<td>36 (13.4%)</td>
</tr>
<tr>
<td>H-retinoblastoma</td>
<td>83 (73.5%)</td>
<td>1.5 (0.8-2.7)</td>
<td>20 (13.4%)</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>248 (65.6%)</td>
<td>1.5 (0.8-2.3)</td>
<td>65 (17.5%)</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>180 (71.9%)</td>
<td>1.5 (0.8-2.3)</td>
<td>27 (12.5%)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>241 (71.9%)</td>
<td>1.5 (0.8-2.3)</td>
<td>26 (12.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>361 (75.0%)</td>
<td>1.5 (0.8-2.3)</td>
<td>27 (12.5%)</td>
</tr>
<tr>
<td><strong>P heterogeneity</strong></td>
<td>0.492</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated with chemotherapy**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>1515 (75.4%)</td>
<td>1</td>
<td>276 (13.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>1035 (69.3%)</td>
<td>0.8 (0.6-1.2)</td>
<td>247 (16.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>446 (73.4%)</td>
<td>0.8 (0.6-1.2)</td>
<td>84 (13.8%)</td>
</tr>
<tr>
<td><strong>P heterogeneity</strong></td>
<td>0.272</td>
<td></td>
<td>0.416</td>
</tr>
<tr>
<td>Treated with radiotherapy† ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>1048 (73.7%)</td>
<td>1</td>
<td>209 (14.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>619 (75.5%)</td>
<td>1.0 (0.8-1.4)</td>
<td>107 (13.0%)</td>
</tr>
<tr>
<td>Brain</td>
<td>662 (72.7%)</td>
<td>1.1 (0.8-1.4)</td>
<td>130 (14.3%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>351 (69.0%)</td>
<td>0.7 (0.5-1.0)</td>
<td>96 (18.6%)</td>
</tr>
<tr>
<td>Abdominal (non-Wilms’)</td>
<td>318 (72.5%)</td>
<td>0.7 (0.5-1.0)</td>
<td>65 (14.4%)</td>
</tr>
<tr>
<td><strong>P heterogeneity</strong></td>
<td>0.236</td>
<td></td>
<td>0.454</td>
</tr>
<tr>
<td>Abdominal (Wilms’)</td>
<td>159 (71.6%)</td>
<td>0.7 (0.5-1.1)</td>
<td>40 (18.0%)</td>
</tr>
<tr>
<td>Abdominal (Wilms’)</td>
<td>192 (66.9%)</td>
<td>0.7 (0.5-1.1)</td>
<td>56 (19.5%)</td>
</tr>
<tr>
<td><strong>P heterogeneity</strong></td>
<td>0.185</td>
<td></td>
<td>0.457</td>
</tr>
</tbody>
</table>

Abbreviations: NHL, non–Hodgkin’s lymphoma; CNS, central nervous system; NH, nonheritable; H, heritable.

*Outcomes evaluated relative to all natural pregnancy outcomes.
†Evaluated relative to all natural pregnancy outcomes plus terminations.
‡Adjusted for decade of treatment.
§Adjusted for premature delivery.
∥Insufficient events to reliably test for heterogeneity.
¶Adjusted for maternal age and birth order.
**Adjusted for treatment with chemotherapy, maternal age, and birth order.
††Convergence not achieved.
‡‡Adjusted for treatment with radiotherapy, maternal age, and birth order.
were excluded from the denominator, as the potential pregnancy outcome for such pregnancies is always unknown. Terminations were expressed as a proportion of all known pregnancy outcomes, specifically the natural outcomes plus all terminations.

To account for potential correlations between pregnancy outcomes of the same survivor, a population-averaged generalized estimating equation modification was used (17). Separate analyses were conducted for female survivors and partners of male survivors. Unless otherwise stated, models were adjusted for maternal age, birth order, and exposure to chemotherapy and radiotherapy variables. Given that general population rates for terminations have changed markedly over the last few decades (18) as well as certain treatment modalities (e.g., introduction of chemotherapy), any association between treatment and the outcome termination may be confounded by decade of treatment; hence, models with termination as the outcome were additionally adjusted for decade of treatment.

To assess live birth rates, we compared the observed number of live born children among survivors to the expected number of live born, for a specified age, based on birth cohort fertility rates of the general population of England and Wales (19). A live birth was considered to be a potential recurrent “event” with the observed number of events having a Poisson distribution. Expected numbers of live births could only be calculated for female survivors, as there were no general population birth cohort fertility rates available for males.

Survivors were asked to provide the reason for the termination, if applicable. The information given was then assigned to one of the categories: possible health problem fetus, social reason, or health problem mother.

The criterion for statistical significance was a P value (two sided) of <0.05. Stata statistical software was used for all analyses (20).

Finally, all analyses were executed on the entire data set and separately on the entire population-based subcohort that excluded the 7% of survivors diagnosed before 1962. There were no important differences observed, except the confidence intervals were somewhat expanded. As there was no evidence of important bias, we included the entire data set in this article.

Results

Pregnancies. Of the 10,483 survivors who completed the questionnaire, 31% reported to have carried or sired at least one pregnancy (n = 3,244) resulting in a total of 7,300 pregnancies. Overall, 6,634 singleton pregnancies were reported, of which 4,113 were produced by female survivors and 2,521 by partners of male survivors.

Table 1 shows the ORs of the different pregnancy outcomes by type of childhood cancer, whether treatment included chemotherapy, and for the different levels of radiotherapy treatment. The odds of producing a live birth did not vary significantly in relation to type of childhood cancer, treatment with chemotherapy, and brain or abdominal radiotherapy.

Likewise, the OR of miscarriage did not vary significantly by cancer type, treatment with chemotherapy.
with different levels of radiotherapy treatment. However, there was a borderline significantly (P = 0.06) increased OR of miscarriage for survivors treated with abdominal radiotherapy [OR, 1.4; 95% confidence interval (95% CI), 1.0-1.9]. This effect was significant when limiting the analysis to miscarriages occurring in gestational week 12 or later (OR, 1.9; 95% CI, 1.1-3.2). No increased risk was observed for miscarriages occurring before week 12 of gestation (OR, 1.0; 95% CI, 0.7-1.5). Treatment with brain radiotherapy was not significantly associated with miscarriages occurring either after or before week 12 (OR, 1.0; 95% CI, 0.6-1.6; OR, 0.9; 95% CI, 0.6-1.3, respectively).

The OR of stillbirth was not significantly related to type of childhood cancer or treatment with radiotherapy. The OR for chemotherapy could not be calculated because of lack of convergence of the regression model (probably due to the rarity of this outcome).

Survivors of heritable retinoblastoma had significantly increased odds of terminating a pregnancy relative to leukemia survivors (OR, 2.1; 95% CI, 1.1-3.7). There was no significant effect of any of the treatment variables on the odds of terminations.

Female survivors treated with abdominal radiotherapy exhibited a significantly increased OR of delivering offspring with a low birth weight (OR, 1.9; 95% CI, 1.1-3.2) adjusted for premature delivery. When those abdominally exposed were separated according to Wilms’/non-Wilms’, then the OR for the Wilms’ group (OR, 2.3; 95% CI, 1.2-4.6) was significantly (P = 0.03) greater than the non-Wilms’ group (OR, 1.6; 95% CI, 0.9-3.0). The percentage of offspring having a low birth weight for women exposed to abdominal irradiation was 22.3% versus 7.6% for women not exposed to irradiation. The latter percentage is comparable with the 7% to 8% observed in the general population of England and Wales (19).

Overall, 28.7% of survivors treated with abdominal irradiation reported a preterm birth versus 10.5% for survivors not treated with any radiotherapy. In relative terms, this corresponds to a 3-fold increased OR (OR, 3.2; 95% CI, 2.1-4.7). Abdominally irradiated Wilms’ tumor survivors showed a 3.5-fold OR (95% CI, 2.1-5.7) of delivering preterm relative to survivors treated without radiotherapy.

Figure 2A shows the ratio of observed over expected number of live births produced by female survivors by type of childhood cancer for all terminations among heritable retinoblastoma survivors were terminated because of reasons relating to the health of the fetus. This percentage was consistent across female and partners of male survivors (data not shown).

Table 2 shows reveals no significant variation in the ORs of any adverse pregnancy outcome by cancer type, exposure to chemotherapy, brain irradiation, or abdominal irradiation.

Reasons for Termination. Table 3 shows that ~70% of all terminations among heritable retinoblastoma survivors were terminated because of reasons relating to the health of the fetus. This percentage was consistent across female and partners of male survivors (data not shown). Among other types of childhood cancer, this percentage never exceeded 14%.

Discussion

Main Findings. This study, the largest population-based investigation into pregnancy outcomes among childhood cancer survivors to date, shows that female survivors of childhood cancer treated with abdominal radiotherapy are at a 3-fold increased risk of delivering preterm and a 2-fold increased risk of delivering low birth weight offspring. Furthermore, there is a risk of miscarriage associated with abdominal radiotherapy but not with brain radiotherapy. Partners of male survivors of childhood cancer are not at risk of adverse pregnancy outcomes. Overall, female survivors produce two thirds the offspring expected and almost half that expected for those treated with abdominal or brain radiotherapy.

Low Birth Weight and Premature Birth. In the current study, female survivors treated with abdominal radiotherapy experienced a 2-fold increased risk of low birth weight. Risks of similar magnitude have previously been reported in non–population-based or smaller-scale studies (6-8). The 3-fold elevated risk we observed for delivering offspring preterm among all female survivors exposed to abdominal radiotherapy is in line with previous findings (8, 11). In our study, Wilms’ tumor survivors had the greatest risk of preterm delivery, which corresponds with previous studies on Wilms’ tumor survivors (10-12). The excess risk of low birth weight and preterm delivery is probably primarily related to the radiation dose to the uterus irrespective of cancer type, but it is difficult to distinguish between treatment effects and cancer type (8). The specific mechanism whereby abdominal irradiation confers an increased risk of delivering preterm and producing offspring with a low birth weight remains elusive. Thus far, a few studies have shown that radiotherapy to the uterus during childhood is associated with reduced adult uterine volume and reduced blood supply of the uterus (21-25). This reduced uterine volume and blood supply may possibly, if a woman is able to conceive at all, restrict fetal growth and the ability to carry the fetus to term.

Miscarriage. The 1.4 increased OR of miscarriage among female survivors treated with abdominal irradiation in our study corroborates the findings by Green et al. (7) who reported a significant 1.65-fold increased risk for female survivors whose ovaries were in or near the
<table>
<thead>
<tr>
<th>Type of childhood cancer</th>
<th>Natural pregnancy outcome*</th>
<th>Termination (n = 190)</th>
<th>Low birth weight (n = 113)§</th>
<th>Premature (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live birth (n = 2,021)</td>
<td>Miscarriage (n = 297)</td>
<td>Stillbirth (n = 13)∥</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%) OR (95% CI)</td>
<td>n (%) OR (95% CI)</td>
<td>n (%) OR (95% CI)</td>
<td>n (%) OR (95% CI)</td>
</tr>
<tr>
<td>Leukaemia (reference)</td>
<td>275 (77.0%) 1</td>
<td>44 (12.3%) 1</td>
<td>2 (0.6%) 1</td>
<td>36 (10.1%) 1</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>227 (78.0%) 0.9 (0.5-1.6)</td>
<td>38 (13.1%) 1.1 (0.6-2.0)</td>
<td>2 (0.7%) 0.9 (0.1-10.0)</td>
<td>24 (8.3%) 1.2 (0.6-2.4)</td>
</tr>
<tr>
<td>NHL</td>
<td>164 (80.0%) 1.1 (0.6-2.0)</td>
<td>25 (12.2%) 0.9 (0.5-1.7)</td>
<td>2 (1.0%) 1.9 (0.3-13.5)</td>
<td>14 (6.8%) 1.0 (0.5-2.1)</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>397 (83.1%) 1.3 (0.8-2.2)</td>
<td>57 (11.9%) 0.8 (0.5-1.3)</td>
<td>0 —</td>
<td>24 (5.0%) 0.7 (0.4-1.5)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>84 (78.5%) 1.0 (0.5-2.1)</td>
<td>17 (15.9%) 1.0 (0.5-2.2)</td>
<td>0 —</td>
<td>6 (5.6%) 0.4 (0.1-2.1)</td>
</tr>
<tr>
<td>NH-retinoblastoma</td>
<td>121 (81.8%) 1.1 (0.5-2.3)</td>
<td>16 (10.8%) 0.9 (0.4-1.9)</td>
<td>1 (0.7%) 1.6 (0.1-17.5)</td>
<td>10 (6.8%) 1.7 (0.7-4.2)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>59 (74.7%) 0.8 (0.4-1.7)</td>
<td>10 (12.7%) 1.2 (0.5-2.7)</td>
<td>1 (1.3%) 3.0 (0.3-33.9)</td>
<td>9 (11.4%) 2.3 (0.8-6.4)</td>
</tr>
<tr>
<td>Wilms' tumor</td>
<td>199 (79.9%) 1.2 (0.6-2.1)</td>
<td>28 (11.2%) 0.8 (0.5-1.6)</td>
<td>2 (0.8%) 1.1 (0.1-12.2)</td>
<td>20 (8.0%) 0.9 (0.4-2.0)</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>118 (78.2%) 0.9 (0.5-1.8)</td>
<td>21 (13.9%) 1.1 (0.6-2.3)</td>
<td>0 —</td>
<td>12 (8.0%) 1.2 (0.6-2.5)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>203 (82.9%) 1.2 (0.6-2.3)</td>
<td>25 (10.2%) 0.7 (0.4-1.5)</td>
<td>3 (1.2%) 2.3 (0.4-14.5)</td>
<td>15 (6.1%) 1.2 (0.5-2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>174 (82.9%) 2.1 (1.0-4.1)</td>
<td>16 (7.6%) 0.5 (0.3-1.0)</td>
<td>0 —</td>
<td>20 (9.5%) 1.5 (0.8-3.0)</td>
</tr>
<tr>
<td>p heterogeneity</td>
<td>0.6 0.699</td>
<td>—</td>
<td>—</td>
<td>0.421 0.522 0.376</td>
</tr>
<tr>
<td>Treated with chemotherapy**</td>
<td>1,173 (83.4%) 1</td>
<td>154 (10.0%) 1</td>
<td>6 (0.4%) 1</td>
<td>73 (5.2%) 1</td>
</tr>
<tr>
<td>No (reference)</td>
<td>583 (76.9%) 0.8 (0.5-1.3)</td>
<td>92 (12.4%) 1.2 (0.7-2.0)</td>
<td>3 (0.4%) 1</td>
<td>80 (10.6%) 1</td>
</tr>
<tr>
<td>Yes</td>
<td>265 (74.2%) —</td>
<td>51 (14.3%) —</td>
<td>4 (1.1%)  —</td>
<td>37 (10.4%) —</td>
</tr>
<tr>
<td>p heterogeneity</td>
<td>0.364 0.451</td>
<td>—</td>
<td>—</td>
<td>0.131 0.971</td>
</tr>
<tr>
<td>Treated with radiotherapy‡‡</td>
<td>639 (81.2%) 1</td>
<td>90 (11.4%) 1</td>
<td>2 (0.3%) 1</td>
<td>56 (7.1%) 1</td>
</tr>
<tr>
<td>No (reference)</td>
<td>572 (81.0%) 1.0 (0.7-1.4)</td>
<td>83 (11.8%) 1.0 (0.7-1.5)</td>
<td>6 (0.9%) 3.4 (0.7-16.4)</td>
<td>45 (6.4%) 1</td>
</tr>
<tr>
<td>Other (nonbrain/abdominal)</td>
<td>355 (79.2%) 1.1 (0.7-1.7)</td>
<td>58 (13.0%) 1.0 (0.6-1.5)</td>
<td>0 —</td>
<td>35 (7.8%) 0.8</td>
</tr>
<tr>
<td>Abdominal</td>
<td>279 (82.1%) 1.1 (0.6-1.8)</td>
<td>38 (11.2%) 0.9 (0.5-1.5)</td>
<td>3 (0.9%) 1.6 (0.2-15.6)</td>
<td>20 (5.9%) 0.7</td>
</tr>
<tr>
<td>p heterogeneity</td>
<td>0.972 0.981</td>
<td>—</td>
<td>—</td>
<td>0.486 0.311</td>
</tr>
<tr>
<td>Abdominal (non-Wilms§)</td>
<td>111 (85.4%) 1.2 (0.5-2.7)</td>
<td>13 (10.0%) 0.9 (0.4-2.0)</td>
<td>1 (0.8%)  —</td>
<td>5 (3.9%) 0.7</td>
</tr>
<tr>
<td>Abdominal (Wilms§)</td>
<td>168 (80.0%) 1.0 (0.6-2.0)</td>
<td>25 (11.9%) 0.9 (0.5-1.7)</td>
<td>2 (1.0%) 1.3 (0.1-12.7)</td>
<td>15 (7.1%) 0.6</td>
</tr>
</tbody>
</table>

*Outcomes evaluated relative to all natural pregnancy outcomes.
†Evaluated relative to all natural pregnancy outcomes plus terminations.
‡Adjusted for decade of treatment.
§Adjusted for premature delivery.
∥Insufficient events to reliably test for heterogeneity.
¶Adjusted for maternal age and birth order.
**Adjusted for treatment with radiotherapy, maternal age, and birth order.
††Convergence not achieved.
‡‡Adjusted for treatment with chemotherapy, maternal age, and birth order.


Pregnancy after Childhood Cancer.

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radiation field. Winther et al. (14) found a 2.8-fold increased proportion ratio for miscarriages among female survivors who received high-dose radiotherapy to the ovaries and uterus relative to sisters, but Chiarelli et al. (6) could not identify an increased risk. When restricting the analysis to miscarriages occurring at or after week 12 of gestation, the risk we observed was more pronounced, but not significantly increased risk was observed for miscarriages occurring before week 12 of gestation.

It has been suggested that radiation to the brain increases the chance of a miscarriage (7) possibly through impairment of the hypothalamic-pituitary-ovarian-axis function (26). Some support for this hypothesis was found by two previous studies. Winther et al. (14) reported a 1.8-fold significantly increased risk of miscarriage among survivors treated with brain irradiation. Green et al. (7) found a 1.4-fold significantly increased risk for survivors treated with brain radiotherapy versus those who did not receive radiotherapy, with the highest risks of miscarriage occurring after week 12 of gestation. We did not find any evidence that brain irradiation confers an excess risk of miscarriage.

Terminations. Overall, there were no strong indications that the OR of a termination varied by cancer type except for female survivors of heritable retinoblastoma for whom the OR was 2-fold relative to leukaemia survivors. This finding suggests that pregnancies among heritable retinoblastoma survivors may be more likely to be terminated as a result of the 50% risk of the fetus inheriting the RB1 gene, which identifies retinoblastoma. Evidence for this is that in our data ∼70% of all pregnancies among heritable retinoblastoma survivors were terminated because of reasons relating to the health of the fetus, a considerably higher percentage than among other survivors.

Live Birth Rate. Recently, Madanat et al. (27) reported a parenthood probability of 0.82 relative to siblings for female survivors of childhood cancer. Syse et al. (28) showed that the probability of a first live birth among female survivors diagnosed with cancer under 10 years of age was 0.69. These observations are comparable with the live birth ratio of 0.64 that we found.

In our study, brain radiotherapy was associated with a deficit of ∼50% in live births compared with the general population. Nygaard et al. (29) found that live birth rates among leukaemia survivors treated with cranial radiotherapy were 0.39 of leukaemia survivors not treated with radiation, which is consistent with our findings. Exposure to cranial radiation has been associated with a decrease in fertility. Green et al. (4) reported 40% less pregnancies among survivors exposed to ≥30 Gy of hypothalamic/pituitary radiation relative to those treated with <10 Gy.

There may be several reasons why survivors produce fewer offspring than the general population, such as treatment-induced ovarian failure (1-3, 30) or early menopause (31-33), more difficulty finding a partner (34, 35), or concerns about the health of offspring (36, 37). However, a detailed investigation into reasons for the reduced live birth rate among survivors is beyond the scope of this article.

Partners of Male Survivors. In this study, there was no evidence that partners of male survivors exhibited an excess risk of adverse pregnancy outcomes. This is consistent with findings from the Childhood Cancer Survivor Study (38), and thus, based on these two studies, any large excess risk among partners of male survivors can be excluded.

Limitations. A limitation of this study concerns the self-reported nature of pregnancy outcomes, which were not independently verified. This may have led to underreporting of pregnancy outcomes, particularly for miscarriages (39). Although any of such underreporting is likely to be unrelated to the “exposure” factors studied here, it cannot be excluded entirely that our findings might have been affected by recall bias. In addition, birth weight data were not reported for 30% of all live born offspring. How this might affect the OR of the exposure factors on the risk of low birth weight is not entirely clear. However, a sensitivity analysis assuming that all offspring for whom birth weight was missing were of low birth increased the OR for abdominal irradiation minimally [from 1.9 to 2.2 (95% CI, 1.4-3.4)]. Similarly, assuming that all offspring with missing birth weight had normal birth weight did not alter the OR appreciably [from 1.9 to 1.8 (95% CI, 1.1-3.1)].

In this study, miscarriage was defined as any pregnancy ending before gestational week 24, whereas in most American studies this was 20 weeks. Theoretically, this could impede comparison of the results across studies.
However, when we excluded miscarriages occurring after week 20 from the analysis, the ORs remained unchanged.

Comparison of miscarriages between our and other studies should therefore be possible.

Lack of comprehensive treatment information did not permit investigating the risk of adverse pregnancy outcomes by dose of radiation received to the reproductive organs; hence, residual confounding by radiation exposure could have distorted the magnitude of the identified risks.

Survivors included in this investigation were treated between 1940 and 1991, and hence, little is known about the potential adverse effects of more recent therapies. Survivors treated more recently are still relatively young and the number of offspring born to these survivors will be relatively small. It is only through continued long-term follow-up of survivors through large-scale prospective cohort studies that it will become clear whether more recent therapies are associated with an excess risk of adverse pregnancy outcomes (40).

Clinical Implications. It is reassuring that the majority of survivors who are able to conceive are not at risk of an adverse pregnancy outcome. However, female survivors who received treatment involving radiation to the reproductive organs, and who are still able to become pregnant, are at risk of an adverse pregnancy outcome and such pregnancies should be monitored and managed by a multidisciplinary specialist team (40).

Conclusion. In conclusion, female survivors of childhood cancer treated with abdominal radiotherapy and who are able to become pregnant are at risk of delivering prematurely and producing low birth weight offspring. Furthermore, there is a risk of miscarriage associated with abdominal radiotherapy but not with brain radiotherapy. Chemotherapy seems not to be associated with any adverse pregnancy outcome. There are no indications of an increased risk of adverse pregnancy outcomes for partners of male survivors. Overall, female survivors produce considerably fewer offspring than the general population, particularly those survivors treated with abdominal or brain radiotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

Pregnancy Outcomes among Adult Survivors of Childhood Cancer in the British Childhood Cancer Survivor Study


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