Abstract. Survival is now the norm for children treated with radiotherapy and chemotherapy for childhood cancers. These children are now living to have children of their own. A Danish study of adverse health outcomes in the offspring of childhood cancer survivors and the offspring of the cancer survivor’s siblings is ongoing. The cumulative probability of congenital malformation is non significantly higher amongst the offspring of cancer survivors than amongst the offspring of cancer survivor’s siblings; and non significantly higher amongst the offspring of cancer survivors who received radiotherapy treatment compared with those who did not. Future analyses will incorporate radiation dose to the uterus and gonads of cancer survivors. To date, studies of childhood cancer survivors’ offspring have not indicated an excess of congenital malformation.

1. Introduction

Whilst 5 year survival after cancer treatment in children is now over 70%, little is known about the troubling possibility that the effects of cancer treatment could be passed onto the next generation. Some survivors become infertile as a result of the treatment, but many are able to have children of their own. The transgenerational effects of the treatment, including the probability of congenital malformation amongst offspring are important issues to be addressed and quantified.

The NCI Five Center Cancer Study [1, 2] evaluated the question of whether cancer treatment can cause birth defects in the offspring of former cancer patients. All the cancer patients were treated before 1976; amongst them the percentage of offspring of survivors with simple malformations was 2.7% (59/2198) and 2.8% (127/4544) for the matched survivors’ sibling controls.

The Childhood Cancer Survivor Study (CCSS) series [3] is larger than the Five Center Cancer Study. In the United States series to date, 4214 children were born to cancer survivors among whom 157 (3.7%) genetic diseases were reported in contrast to 95 (4.1%) reported conditions among 2339 children born to sibling controls. In the Denmark series, with cancer survivors and their siblings included through to the end of 1996, the comparable figures were 82 (6.1%) birth defects among 1345 children of cancer survivors and 211 (5.0%) among 4225 children of sibling controls. Coupled with prior studies, these preliminary findings, if sustained by ongoing dose-response analyses, provide reassurance that cancer treatments including radiotherapy do not carry much if any risk for inherited genetic disease in offspring conceived after exposure.

In 1947 a surveillance of all pregnancy outcomes after 20 weeks of gestation was begun in the cities of Nagasaki and Hiroshima. The early genetic study focussed on the clinical assessment of the health of children born in these two cities to the survivors and to unexposed parents. The statistical analyses of 69706 pregnancy outcomes found that the frequency of malformations is not significantly associated with joint parental exposure [4].
Adverse pregnancy outcomes including congenital malformations in offspring might, in theory, be related to constitutional genetic disorders in survivors that were associated with their cancers or to germ cell mutagenesis from radiotherapy or cytotoxic drugs. Among women, radiotherapy or surgical procedures that damage the uterus can also increase the risk of deformed children related to growth inhibition. Survivors from cancer in youth now form the largest group of people exposed to high doses of potential mutagenetic agents before reproduction.

2. Patients and methods

This is a population based nationwide Danish cohort study. The cumulative probability patterns of malformations amongst the offspring of childhood cancer survivors are contrasted with the cumulative probability patterns in the offspring of healthy siblings of the childhood cancer survivors. Furthermore, the cumulative probability patterns of malformations in the offspring of childhood cancer survivors treated with radiotherapy are compared with those not treated with radiotherapy. Survival data analysis methods [5, 6, 7] have been used in these analyses. S-PLUS was the software used to produce the graphs of the cumulative probability of congenital malformation with attained age of the child and the Cox regression analyses for Table I. S-PLUS code indicating how FIG. 3 Graph a) and Table I a) were produced is given in the Appendix. Plots of martingale residuals, deviance residuals and scaled changes in the coefficients have been examined as part of the analysis, with the S-PLUS cox.zph function used to test the proportional hazards assumption.

3. Childhood cancer survivors

The Danish Cancer Registry (DCR) files were used to identify all cancer patients diagnosed under the age of 25 years between the beginning of the cancer registration system in 1943 and the end of 2001. The DCR files were also used to provide the Danish citizen’s unique personal identification number which provides a link between the registries. This study included only cancer patients (1083) who survived until the start of the national Central Population Registry (CPR) in 1968 (when all Danish citizens were assigned their unique personal identification number) or who were born after that date and became parents during the period 1977-2001, when malformations amongst children were well registered. The possibility of including the cohort of all patients born before 1977 (and their siblings) was dismissed on the basis that their first congenital malformation would most likely not be registered and their experience could therefore not be systematically included as left truncated experience from 1.1.1977 onwards.

4. Childhood cancer survivors’ siblings and offspring

The CPR was searched for all 1083 registered parents and thereby identified 3059 healthy siblings who were alive at, or born after, the start up of the CPR in 1968. Through further searches in the files of the CPR, 1879 offspring of the childhood cancer survivors and 6037 offspring of their healthy siblings were identified.

5. Identifying congenital malformations amongst the offspring

Only children born in Denmark between the start of Hospital Discharge Registry (HDR) in 1977 and the end of 2001 were included. Files of the HDR were used to identify all malformed children of childhood and adolescent cancer survivors and of their siblings. Congenital Malformations are defined as International Classification of Disease (ICD) 8/9 codes 740-759 and ICD 10 codes Q00-Q99. Gender dependent congenital malformations are defined as ICD8/9 code 752 and ICD 10 codes Q50-Q56, ie gonadal malformations primarily retention testis and hypospadia among male offspring. A total of 112 and 303 malformations were registered among survivors and among their siblings, respectively.
6. Exposure to radiotherapy

The DCR was used to obtain information on the radiotherapy treatment (yes/no) for the total cohort of survivors who became parents.

7. Notation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOM.ID/DAD.ID</td>
<td>Identity number of mother or father of the survivor/sibling</td>
</tr>
<tr>
<td>CHILD.ID</td>
<td>Identity number of child of survivor/sibling (last digit even if female and odd if male)</td>
</tr>
<tr>
<td>mal</td>
<td>Congenital malformation registered (mal=1 if yes; mal.sex=1 if gender dependent malformation)</td>
</tr>
<tr>
<td>Exit</td>
<td>Number of days to the end of follow up since Start day 0</td>
</tr>
<tr>
<td>RADIO</td>
<td>Radiotherapy treatment of index patient (yes/no), no is the reference group</td>
</tr>
<tr>
<td>INDEX.ID</td>
<td>Identity number for index patients (childhood cancer survivors) or a sibling of the survivor (last digit even if female and odd if male)</td>
</tr>
<tr>
<td>INDEX</td>
<td>I = index patient (childhood cancer survivor), the reference group</td>
</tr>
<tr>
<td>S</td>
<td>Sibling of childhood cancer survivor</td>
</tr>
<tr>
<td>GENDER.P</td>
<td>=1 if Male (INDEX.ID odd) =2 if Female (INDEX.ID even)</td>
</tr>
<tr>
<td>GENDER.C</td>
<td>=1 if Male (CHILD.ID odd) =2 if Female (CHILD.ID even)</td>
</tr>
<tr>
<td>BORDER.C</td>
<td>Birth ordering of offspring within INDEX.ID</td>
</tr>
<tr>
<td>OFFSIZE.C</td>
<td>Number of offspring to INDEX.ID</td>
</tr>
<tr>
<td>INDEX.AGE</td>
<td>Age of index parent at birth of offspring (mean age of 28.5 years subtracted)</td>
</tr>
<tr>
<td>BYEAR.C</td>
<td>Birth year of offspring (1989 as year 0)</td>
</tr>
</tbody>
</table>

FIG. 1, the family map, illustrates the structure of the data set. Following the left hand part of the diagram 360 irradiated survivors (INDEX=I, identity number INDEX.ID, RADIO=yes) are children of MOM.ID/DAD.ID. They have had 619 offspring and 41 of these offspring have been registered for a congenital malformation (mal=1). See family map for fuller details.

8. Hypotheses under investigation

Under test are two hypotheses relating to differences in the cumulative probability patterns of congenital malformation with attained age: between the offspring of survivors and siblings; and for the offspring of survivors, between those treated with radiotherapy and those not treated with radiotherapy.

9. Results

Results are presented from an ongoing population based nationwide Danish study comparing patterns of cumulative probability of first registration for congenital malformation with attained age of offspring. The total number of 7916 offspring included comprises 1879 offspring of Danish cancer survivors and 6037 offspring of the survivors’ siblings, born in the period 1.1.1977 through to 31.12 2001 inclusive. The offspring have been followed up to the earlier of: death, end of study (31.12.2001), age 25 years or date of first registration for congenital malformation. Results are presented for some Kaplan-Meier plots as FIG. 2 Graphs a) and b) and FIG. 3 Graphs a), b) and c) and for Cox regression models in Table I. It might be noted that although malformations are present at birth, up to 30 percent are not noticed or recorded at birth. Thus a survival analysis was conducted accounting for the varying ages at which the malformations were recorded.
9.1 Exclusion of Gender Dependent Malformations

A comparison of FIG. 2 a) with FIG. 2 b) shows that the statistically significant difference in the cumulative probability for all congenital malformations amongst the 7916 offspring of survivors and of siblings for the males versus female offspring (log rank statistics of 20.6 compared with 0.3) is driven by the inclusion of the 88 gender dependent (86 in male offspring and 2 in female offspring) congenital malformations. Once these gender dependent congenital malformations are (treated as) censored at the event (Exit) time, no statistically significant difference in the cumulative probability of non-gender dependent congenital malformations exists between male and female offspring (FIG. 2b). The Graphs of FIG. 3 for the 1879 offspring of survivors and the Table I results use the non-gender dependent congenital malformations (mal-mal.sex) as the event.

9.2 Testing the Hypotheses

For the Table I a) model analyses using all the 7916 offspring there are no indications of departures from the proportional hazards assumption. Table I a) shows that there is a non-significantly higher hazard rate of non-gender dependent congenital malformations for the offspring of childhood cancer survivors compared with the offspring of their siblings. From the relationship between survivor functions with variables under the Cox model and baseline survivor functions, it follows that the cumulative probability of non-gender dependent congenital malformations will be non significantly higher for the offspring of childhood cancer survivors compared with the offspring of their siblings.

However, for the Table I b) model analyses using the 1879 offspring of survivors, cox.zph results show that there is a significant departure (p <0.020) from proportional hazards for GENDER.C, significant for the univariate model and illustrated by the converging “staircase” steps in FIG. 3 Graph a). Table I b) also shows that there is a non-significantly higher hazard rate of non-gender dependent congenital malformations for the survivors treated with radiotherapy compared with the offspring not so treated (FIG. 3 Graph c). The near statistical significance for GENDER.P is indicated in FIG. 3 Graph b).

Conclusions

Although there is some merit in the comparisons of the crude rates of congenital malformations amongst the offspring of survivors treated by radiotherapy (41/619) with survivors not treated by radiotherapy (71/1269) and with survivor’s siblings (303/6037), survival methods provide a far better means of gaining insight into the data. The analysis of the Danish Childhood Cancer Survivors Study data set shows that the cumulative probability of non-gender congenital malformations is non significantly higher amongst :-

The offspring of cancer survivors than amongst the offspring of cancer survivor’s siblings;

The offspring of cancer survivors who received radiotherapy treatment than the offspring of cancer survivors who did not receive radiotherapy treatment.

Although chance could not be excluded as a reason for these differences, future work will take into account radiation dose to the gonads and uterine tissue, and the study will be expanded to incorporate data from the ongoing CCSS series [3]
References


FIG. 1. *Family Map for All Congenital Malformations*

[Diagram showing the family map with nodes and conditions]
FIG 2. Kaplan-Meier cumulative probability of malformation being recorded by age of child for gender of children born to both survivors and siblings: Graph a) all congenital malformations, Graph b) non-gender dependent malformations.

Log rank Statistics: Graph a) = 20.6, Graph b) = 0.3, both with 1 degree of freedom
FIG 3. Kaplan-Meier cumulative probability of non-gender malformation being recorded by age of child: Graph a) for gender of child born of survivors, Graph b) for gender of the cancer survivors.

Log rank Statistics: Graph a) = 0.6 Graph b) = 2.6, both with 1 degree of freedom
FIG 3. Kaplan-Meier cumulative probability of non-gender malformation being recorded by age of the child: Graph c) for radiotherapy status of the cancer survivor.

![Graph c) Stratified by Radiotherapy Treatment](image)

Log rank Statistic : Graph c) = 0.2, with 1 degree of freedom.

Table I: Hazard rate estimates of congenital malformations for study variables for a) all children of cancer survivors and siblings b) for children of cancer survivors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>coef</th>
<th>exp(coef)</th>
<th>Standard Error</th>
<th>p-value</th>
<th>coef</th>
<th>exp(coef)</th>
<th>Standard Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) All 7916 Offspring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INDEX</td>
<td>-0.103</td>
<td>0.902</td>
<td>0.128</td>
<td>0.42</td>
<td>---</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>GENDER.C</td>
<td>0.065</td>
<td>1.067</td>
<td>0.111</td>
<td>0.56</td>
<td>0.201</td>
<td>1.222</td>
<td>0.216</td>
<td>0.35</td>
</tr>
<tr>
<td>GENDER.P</td>
<td>-0.174</td>
<td>0.841</td>
<td>0.116</td>
<td>0.14</td>
<td>-0.447</td>
<td>0.640</td>
<td>0.233</td>
<td>0.06</td>
</tr>
<tr>
<td>OFFSIZE.C</td>
<td>-0.030</td>
<td>0.971</td>
<td>0.074</td>
<td>0.69</td>
<td>0.202</td>
<td>1.224</td>
<td>0.149</td>
<td>0.18</td>
</tr>
<tr>
<td>BYEAR.C</td>
<td>-0.017</td>
<td>0.983</td>
<td>0.010</td>
<td>0.08</td>
<td>-0.011</td>
<td>0.989</td>
<td>0.016</td>
<td>0.49</td>
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<tr>
<td>BORDER.C</td>
<td>-0.045</td>
<td>0.956</td>
<td>0.098</td>
<td>0.65</td>
<td>-0.340</td>
<td>0.712</td>
<td>0.191</td>
<td>0.07</td>
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<tr>
<td>INDEX.AGE</td>
<td>0.003</td>
<td>1.003</td>
<td>0.014</td>
<td>0.83</td>
<td>0.031</td>
<td>1.031</td>
<td>0.026</td>
<td>0.24</td>
</tr>
<tr>
<td>RADIO</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0.104</td>
<td>1.110</td>
<td>0.225</td>
<td>0.64</td>
</tr>
</tbody>
</table>

b) 1879 Offspring of Survivors
Appendix

For FIG. 3 Graph a)

Compute the coxph object fit.genderc

fit.genderc<-coxph (Surv(Start, Exit, mal) ~ strata(GENDER.C), data= data.frame)

Compute the Kaplan-Meier survival curve from the coxph object fit.genderc

fit<-survfit(fit.genderc, type="kaplan-meier")

Extract the time points and corresponding estimates of the survival probabilities

gendercdf<-data.frame(summary.survfit(fit)$time, summary.survfit(fit)$surv)

Calculate the number of time points in each strata

genderctbl<-table(summary.survfit(fit)$strata)

Then plot 1-survival probabilities using the “staircase” option against the time points within each of the strata and survdiff is used to produce the log rank statistics [6].

For Table I  a)

Compute the Cox regression model results using

fit<-coxph (Surv(Start, Exit, mal-mal.sex) ~INDEX+GENDER.C+GENDER.P+OFFSIZE.C+BYEAR.C+BORDER.C+INDEX.AGE, data=data.frame)