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Preterm Delivery Among Female Survivors of Childhood, Adolescent and Young Adulthood Cancer

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Abstract

We studied the deliveries of female cancer survivors and female siblings in a population-based setting in Finland. Nationwide cancer and birth registries were merged to identify 1309 first post-diagnosis deliveries of early onset (diagnosed under age 35) female cancer patients and 5916 first deliveries of female siblings occurring in 1987–2006. Multiple logistic regression models were used to estimate risk of preterm (<37weeks), low birth weight (LBW) (<2500g), and small-for-gestational-age (SGA) deliveries.

The risk of preterm delivery among cancer survivors compared to siblings was overall elevated (Odds ratio (OR) 1.46, 95% confidence interval (CI) 1.14–1.85), the increase in risk being visible in all diagnostic age groups. Risk of LBW was also significantly increased (OR 1.68; 95% CI 1.29–2.18) but not after adjustment for duration of pregnancy (OR 1.11; 95% CI 0.76–1.64). Neither was the risk of SGA increased. The risk of preterm delivery was most pronounced in survivors delivering ten years or more after diagnosis. Site specific analyses indicated that survivors of germ cell tumors and central nervous system (CNS) tumors were at increased risk of preterm delivery, although numbers were small. In childhood survivors, kidney tumors formed the main cause of preterm delivery.

Pediatric, adolescent and young adult cancer survivors are at risk for preterm delivery. Heightened surveillance is recommended especially for Wilms', germ cell and CNS tumor survivors. Such adverse pregnancy outcomes can occur a decade or more after cancer diagnosis indicating a continued need for obstetric awareness, surveillance and counseling in former cancer patients.

Keywords

Preterm; Cancer survivors; Pregnancy; Late-effects

With the improvement of diagnostics and treatment, over the past decades, more patients with early onset cancer survive. According to some estimates, five-year survival rates have reached up to 81% among pediatric patients (aged 0–14 years at diagnosis) and 87% among

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Adolescent and young adult cancer survivors are at risk for preterm delivery as are pediatric cancer survivors. An emphasis should be placed on continued surveillance and obstetric follow-up of survivors as far as a decade or more after diagnosis.

adolescent and young adult (aged 15–24 years) patients¹. Thus parenthood is possible for an expanding number of cancer survivors^{2, 3}. This raises questions regarding the potential effects of cancer and its treatments on pregnancy, neonatal outcomes and health of offspring.

Cancer survivors face anxiety and fears relating to reduction in overall fertility, possible pregnancy risks, as well as health effects in offspring⁴. Many previous studies on the health of offspring are hospital-based and focus on a limited subgroup of cancer patients^{5, 6}. Moreover, most studies are limited to the offspring of pediatric cancer survivors^{7, 8}.

Cancer survivors represent the largest group of people of reproductive age exposed to a wide range of ionizing radiation doses to the gonads as well as to genotoxic chemotherapeutic agents⁹. While some adverse reproductive outcomes (e.g. stillbirths, spontaneous abortions and cytogenetic abnormalities) in female cancer survivors are hypothesised to result from germ cell toxicity caused by mutagenic exposures, others (e.g. preterm delivery and low birth weight) have been shown to be linked to direct radiation-induced damage to the vasculature and elastic properties of the uterus incurred by abdomino-pelvic radiation¹⁰.

One multi-institutional study on female childhood cancer survivors showed patients to be at an increased risk for preterm delivery and low birth weight in a manner directly related to dose to the uterus from radiotherapy¹⁰. Other population-based studies in different countries have confirmed this result^{8, 11–14}. A Norwegian study¹² examined parenthood among male and female cancer survivors aged 15–45 years at diagnosis and perinatal health of their offspring. This study found both the risk of preterm delivery and low birth weight of offspring to be increased among female cancer survivors compared to the risk among the general population retrieved from the Medical Birth Registry. A Scottish study¹¹ identified all post-diagnosis first deliveries of former female cancer patients aged 35 years or less at diagnosis. In addition to an elevated risk of preterm delivery, the study found that cancer survivors were at an elevated risk of operative delivery compared to a randomly selected comparison population.

An early study of primarily Wilms' tumour survivors collected information on pregnancy outcomes by a postal survey and found an elevated proportion of adverse pregnancy outcomes (spontaneous abortion, low birth weight) among abdominally irradiated patients compared to unexposed patients diagnosed with the same malignancy¹⁵. Other similar studies have published consistent reports^{6, 16–18}. Recent studies on larger cohorts of childhood cancer survivors have found an elevated risk of adverse pregnancy outcomes in patients treated with radiotherapy for a wide range of malignancies^{8, 10, 13, 14}. In a questionnaire-based study in Ontario, Canada, Chiarelli et al. reported that in addition to preterm birth and low birth weight, infants born to patients who had received abdominal-pelvic irradiation were also at higher risk of perinatal death compared to offspring of those treated with surgery only¹⁴. Signorello et al. found an increased risk of preterm delivery and low birth weight among children of patients treated with high-dose radiotherapy to the uterus (>500cGy) compared with the children of survivors who did not receive radiotherapy¹⁰. Mueller et al., using a registry-based approach, reported an increased risk of preterm delivery and low birth weight not only in irradiated patients, but also in those receiving chemotherapy only¹³. Reulen et al., in a population-based questionnaire study in the United Kingdom, found female survivors exposed to abdominal irradiation to be at a 3-fold risk of delivering prematurely, a 2-fold risk of delivery of a low birth weight infant and a slightly increased risk of miscarriage⁸. Green et al. explored, in addition to low birth weight, the risk of various other pregnancy outcomes including live births, stillbirths, miscarriages, abortions following treatment with radiotherapy and a wide range of chemotherapeutic agents¹⁹. Although no increased risk of adverse pregnancy outcomes was associated with any chemotherapeutic agent, risk of low birth weight was associated with

pelvic irradiation. In Denmark, Winther et al. reported a significant increase risk of spontaneous abortions associated with high-dose radiotherapy to the ovaries and uterus among female survivors of childhood cancer²⁰.

Using a nationwide population-based approach in Finland, we explored whether the risk of adverse pregnancy outcomes was elevated among female cancer survivors diagnosed in childhood (0–14 years), adolescence (15–19 years) or early adulthood (20–34 years) in Finland. Using a registry-based approach for obtaining pregnancy information and obstetric histories of cancer patients and a comparison group of siblings, our specific goals were to estimate the risk of preterm birth, low birth weight and restricted fetal growth in early onset cancer survivors (groups that until recently are not often included in health outcome research) and to evaluate the effect of time from treatment to delivery.

Materials and Methods

Each individual living in Finland has a unique personal identification number (PIN) since the late 1960s, which enables merging of data for individuals alive in 1969 or born thereafter. This retrospective cohort analysis used data derived from linkage between the population-based, nationwide Finnish Cancer Registry (FCR), Central Population Registry (CPR), and the Medical Birth Registry (MBR).

The FCR began systematic registration in 1953 and data are almost complete (100% for solid tumors, over 90% for hematological malignancies, and 100% for childhood cancers)²¹. In the FCR, information on treatment, when available, is based on clinical notifications and includes data on radiotherapy, chemotherapy and surgery. Details of the anatomical region irradiated, dose or in the case of chemotherapy dose and agent administered are not included. Details on coded treatment data are as follows: palliative/radical/radicality unknown and during the first four months/after the first four months/timepoint unknown.

The CPR, founded in 1969, is nationwide and includes the name and former names, PIN, municipality of birth and residence, date of emigration, or date of death of all Finnish citizens and permanent residents in Finland. The MBR contains, from 1987 onwards, data on all mothers giving birth and on all children born in Finland. All live- and stillbirths at a birth weight of at least 500g or a gestational age of at least 22 weeks are included in the registry. The data are received from the hospitals of delivery or from the midwife or physician assisting in the delivery. Data for less than 0.5 per cent of infants are missing in the MBR²², but information on these cases with missing MBR data is routinely collected within the CPR.

Preterm delivery was defined as a birth occurring at less than 37 full weeks (<37weeks) of gestation and early preterm delivery as less than 34 weeks (<34weeks) of gestation. In the MBR, the best clinical estimate of gestational age at birth is reported in weeks and days, but in this study, only full weeks were used. A low birth weight (LBW) infant was defined as a neonate weighing less than 2500g at birth. Small-for-gestational-age (SGA) was defined as having a birth weight on the -2SD (standard deviation) curve or below compared to infants of the same sex born during the same gestational week using the national birth weight statistics²³. Information on the potential confounding variables of maternal age, maternal smoking, maternal hypertension, maternal infection, maternal diabetes, pre-eclampsia, placental problems, delivery year, child sex, malpresentation, caesarean delivery and use of artificial reproductive technology were available from the MBR for survivors and siblings alike.

The cancer survivor cohort was identified from the records of the FCR. All patients diagnosed with a malignant neoplasm between 1st of January 1953 and 31st of December

2004 and aged 0–34 years at diagnosis were identified³. By linkage to the CPR, female full- and half-siblings of the cancer patients were identified. By further linkage to the MBR we identified all offspring of female cancer patients and of female siblings. For both patients and siblings, only singleton live-births occurring from 1987 to the end of 2006 were included. In the study, the vast majority of patients, 97.4%, were diagnosed with cancer after 1970 and 85.5% after 1980. The MBR contains information on the birth order of the child in the family for mothers registered since 1987, even for births occurring prior to 1987. Children born before 1987 are excluded because details of birth weight, gestational age and other characteristics could not be obtained; however, birth order of all children is known for both survivors and siblings and is adjusted for in analyses including all post-diagnosis offspring for patients and all offspring for siblings. Moreover, for patients, only births occurring at least 9 months after the parent's diagnosis were included in order to exclude those women whose cancer was diagnosed during pregnancy and offspring born before diagnosis.

As parity is expected to have an influence on birth-weight and primiparity is a known risk factor for preterm delivery²⁴, only first deliveries of cancer survivors and siblings were included in the main analyses, thus eliminating any influence of previous obstetric history on the end points studied. Furthermore, as twin and triplet deliveries are strongly associated with the outcomes studied, only singleton deliveries were included.

Multiple logistic regression modeling was used to calculate odds ratios (OR) as measures of relative risk for the dichotomous outcomes of preterm birth, LBW and SGA among first live-born offspring. Additional analyses including stillbirths were also performed. As data were available on a large number of exposures during pregnancy that are potential risk factors for an adverse pregnancy outcome and therefore possible confounders (Table 1), the log likelihood ratio test was used to identify those explanatory variables to be included in the final model. Despite the a priori decision to include maternal infection, maternal diabetes or impaired glucose tolerance, pre-eclampsia and decade of diagnosis, in our data these did not prove to have an effect on the outcomes studied. Models for assessing low birth weight were also adjusted for full gestational weeks at delivery as a continuous variable. Maternal age, year of delivery and socioeconomic status were defined as categorical variables. All other variables adjusted for were dichotomous.

By combining the available information on the site of the tumor and whether the initial treatment included radiotherapy, survivors were classified into 4 mutually exclusive groups: no radiotherapy, abdomino-pelvic radiation, cranial radiation, radiotherapy other than to the brain or the abdomino-pelvic region. To study the possible effect of treatment other than radiotherapy a separate analysis of the patients who had not received ionizing radiation as part of their therapeutic exposure resulted in the following groups: chemotherapy with or without surgery and surgery only.

For the preterm birth outcomes, analyses including all post-diagnosis singleton births of cancer patients and all singleton births of siblings were also performed. In addition to the previously mentioned explanatory variables, these models were also adjusted for birth order, previous history of an early preterm delivery at <34 weeks, previous history of stillbirths, and spontaneous or induced abortions. As more than one pregnancy per subject were included in these analyses, conditional fixed-effects logit models²⁵ were applied to take into account the dependent nature of the data for children born to the same subject.

Defining socioeconomic status for young women is difficult, since many of them are not in the labour market, therefore data on socioeconomic status were missing in more than 30% of

cases. We checked models adjusting for this variable and since the results did not differ materially, the final models are presented without adjustment for socioeconomic status.

In a separate analysis, female patients were also matched to their female siblings and conditional logistic regression modeling was used to produce ORs for the main outcomes. The results were in agreement with those using non-matched data, although, most ORs lost their significance due to reduced sample size in matched analyses, i.e., matching limited the sample size to 12% (392 patients and 504 sibling contributed to the 392 matched sets) of the entire data available. Results are presented for the non-matched data.

Checking for possible interactions between the variables in each model was based on the likelihood ratio test. All interactions among the variables in the final model were checked and none were found to be significant. Estimates of model parameters and 95% confidence intervals (CI) were computed by the maximum likelihood technique.

Analyses on firstborn children were conducted on the entire data and separately on the sub-cohort that excluded the 2.6% diagnosed before 1970. As no major differences were observed, final analyses included only deliveries of mothers diagnosed after 1970. Because the MBR came into existence in 1987, we recognize that not all firstborn children are included in these analyses.

Results

Descriptive characteristics of pregnancies of patients and siblings are displayed in Table 1. A total of 9079 women with first deliveries were identified (Figure 1). Of these, 2880 were cancer survivors and 6199 were siblings. After excluding multiple deliveries, pregnancies which resulted in a stillbirth and those occurring before or within 9 months of a patient's diagnosis, 1309 deliveries of patients and 5916 deliveries of siblings, with information on possible explanatory variables, were eligible for the analyses.

Of the eligible cancer survivors, 297 (22.7%) were diagnosed with cancer in childhood (0–14 years), 249 (19.0%) in adolescence (15–19 years) and 763 (58.3%) in young adulthood (20–34 years). The distribution of primary site of cancer by age at diagnosis of women experiencing a first post-diagnosis delivery is shown in Table 2. Most childhood cancer survivors were leukemia patients, whereas malignant epithelial neoplasm patients formed the majority of adolescent and young adulthood cancer survivors.

Overall, the risk of preterm delivery and early preterm delivery was elevated among female cancer survivors compared to female siblings (Table 3). This elevation was still significant after adjustment for the main confounders. The crude risk of delivering a LBW infant was significantly increased but not after adjustment for duration of pregnancy. The risk for delivery of a small-for-gestational age infant was not elevated among female cancer survivors.

In analyses grouped by age at cancer diagnosis, mothers diagnosed in childhood or as young adults were at a significantly increased risk for preterm delivery, this being more pronounced among survivors of pediatric cancer (Table 4). Among survivors of adolescent cancer, the risk for delivering at less than 37 weeks was also elevated, although not significantly (Table 4). Risk of having a preterm delivery was elevated in all cancer diagnostic age-groups; after adjustment the risk was significantly elevated only among childhood cancer survivors. A significantly elevated risk of LBW was observed among pediatric and young adult cancer survivors in crude analyses. After adjusting for gestational age a non-significant elevation in risk among childhood survivors remained, while the

association disappeared for young adults. Results of SGA risk did not vary by diagnostic age group (Table 4).

It appeared that time from diagnosis to delivery was an important determinant of risk for preterm delivery and LBW (Table 5). In pediatric and young adult cancer survivors delivering more than 10 years from diagnosis, the risk of preterm delivery was doubled compared to siblings. It is noteworthy, however, that in this subgroup only 8/22 of pediatric patients had received radiotherapy, while the equivalent proportion among young adult cancer survivors delivering prematurely was 8/10. Among pediatric and adolescent survivors, risk of early preterm delivery was elevated among those delivering later than 10 years from diagnosis, though significantly only among pediatric patients. Similarly, the risk of delivering a LBW infant was elevated for those pediatric and young adult cancer survivors delivering at ten or more years after diagnosis, though non-significantly (Table 5).

Despite small numbers in most cancer sites (Table 6), risk of preterm delivery was significantly elevated among survivors of kidney tumors (OR 5.50, 95% CI 2.39–12.64) and germ cell tumors (OR 2.94, 95% CI 1.38–6.25). Also, risk of early preterm delivery was increased in survivors of brain and central nervous system tumors (OR 2.67, 95% CI 1.04–6.87) as well as kidney tumors (OR 9.31, 95% CI 2.93–29.57). The risk of LBW was elevated, though not significantly, in survivors of kidney tumors (OR 2.74, 95% CI 0.63–12.03). All kidney tumor patients delivering prematurely were diagnosed in childhood with Wilms' tumors, whereas 3 out of 9 germ cell tumor survivors with a preterm delivery were diagnosed in adolescence and 6 in adulthood. Early preterm delivery occurred in a total of 5 CNS tumor survivors, 2 of which were diagnosed in childhood, 2 in adolescence and 1 in adulthood.

We also performed the analyses excluding the above mentioned high risk diagnostic subgroups one at a time. The risk of preterm delivery among pediatric cancer survivors was no longer significantly elevated after excluding the Wilms' tumor patients (OR 1.26, 95% CI 0.76–2.08). The same was true for adulthood survivors after excluding the high risk subgroup of germ cell tumor patients (OR 1.29, 95% CI 0.94–1.77).

Overall, patients receiving radiotherapy treatment were at an elevated risk of preterm delivery compared with siblings (OR 1.49; 95% CI 1.03–2.16) as 36/434 survivors in this treatment subgroup delivered at <37 weeks (data not shown). Abdomino-pelvic irradiation increased the risk of preterm delivery as 13 out of 72 survivors treated in this way delivered prematurely (OR 3.81; 95% CI 2.02–7.19). Cranial irradiation and radiation directed at other sites were not associated with an increased risk of the outcomes studied. The elevation in risk of preterm delivery was visible in 7/37 pediatric (OR 4.01, 95% CI 1.71–9.40) and 3/14 adolescent cancer survivors (OR 5.44, 95% CI 1.45–20.48) who had received abdomino-pelvic irradiation, but not significantly in adult cancer patients receiving the same exposure (3/21; OR 2.44, 95% CI 0.67–8.92). Interestingly, however, in the young adults age-group, risk of preterm delivery was significantly elevated among 37/452 patients whose treatment regimens did not include radiotherapy (OR 1.49; 95% CI 1.03–2.15).

Among patients who did not receive radiotherapy, chemotherapy was associated with a significantly elevated risk of preterm delivery as 19/155 receiving chemotherapy had a preterm delivery (OR 2.42, 95% CI 1.45–4.05). Out of 598 patients receiving surgery alone, however, only 43 had a preterm delivery and were not at a significantly elevated risk of preterm delivery (OR 1.33, 95% CI 0.95–1.87).

Although overall results did not change substantially, in analyses including stillbirths, the risk of early preterm delivery was significantly elevated among young adulthood cancer survivors, and specifically among those delivering within ten years of diagnosis. It is

noteworthy that of the 5 stillbirths among cancer survivors, 4 were preterm deliveries occurring at <34 weeks (3 among young adult survivors and 1 in an adolescent cancer survivor).

After matching patients with their biological half- or full siblings, the risk of preterm delivery was still significantly elevated among former cancer patients.

For the outcomes of preterm and early preterm deliveries, additional analyses including all post-diagnosis deliveries resulted in similar results as those including only the first post-diagnosis delivery (data not shown).

Discussion

Overall, previous history of cancer places females at an elevated risk for preterm delivery^{10–12}. In our study, cancer survivors had a 50% increased risk of delivering before 37 full weeks of gestation. Age at cancer diagnosis was an important determinant of this risk; pediatric patients had a 62% increased risk and young adults a 36% increased risk compared with the sibling comparison group. Furthermore, we found the risk of preterm delivery to be high also in survivors delivering a long time from cancer diagnosis in all age groups. Results were similar when all post-diagnosis deliveries were included in analyses and adjustment for birth order was made.

A novel finding in our study was that the risk of preterm delivery was also elevated among adolescent and young adulthood cancer survivors, and not associated solely with radiotherapy exposure in young adults. Previously, most reports have included survivors of cancer in childhood or in a restricted subgroup of survivors^{6, 26}. Two recent studies, however, extended the age range of cancer survivors by including patients aged 15–35 years¹² and 0 to 43 years¹¹ at diagnosis, but results for young adults were not reported separately. In our study, adult cancer survivors were not likely to deliver LBW infants after adjusting for gestational age.

A second finding not previously reported, was that deliveries occurring more than 10 years after diagnosis were more likely to be preterm. Radiation induced fibroatrophy is a late effect of radiotherapy, which may take years to develop²⁷. This may explain the finding, as the elasticity of uterus is more likely to be restricted by fibroatrophic changes a decade or more after treatment. The extent to which radiotherapy explains the elevated risk observed with increasing time lag from diagnosis to first delivery is not entirely clear as although the majority of young adult patients delivering prematurely had received radiotherapy while pediatric patients with the outcome were mainly non-irradiated according to FCR data. Another possible explanation could be the differential effect of age on obstetric risk factors. Although adjustment for age at delivery takes into account the observed higher age of patients at first delivery (Table 1), the possibility that increased maternal age poses a higher obstetric risk for patients than for siblings cannot be dismissed. This is implied by previous studies showing that cancer survivors suffer a wide range of metabolic problems over time²⁸. Another contributing factor may be that women in this subgroup, due to higher maternal age, experience more problems with conception and achieving pregnancy, possibly requiring more assistance from reproductive technologies, which as such have been associated with the outcomes studied²⁹.

A third notable finding in our study relates to the site specific risk estimates. We found an increased risk of preterm delivery among mothers who survived a germ cell tumour and a tumour of the Central Nervous System (CNS). With most CNS cancer survivors, the amount of scatter radiation from the treatments to the head and neck region to the reproductive organs cannot be considered substantial to cause meaningful uterine damage, and thus a

possible effect on the hypothalamo-pituitary axis may contribute to the premature initiation of labor. In addition, in some CNS tumors, administered spinal irradiation may be responsible for direct uterine effects. Chance associated with small numbers, however, may play a role since a similar association was not seen in a study of pregnancies among childhood cancer survivors¹⁰.

Among the 56 cancer survivors with germ cell malignancies (45 with ovarian cancer), all 7 mothers with preterm deliveries received chemotherapy and none was irradiated. Furthermore, the overall result of an elevated risk of preterm delivery among survivors receiving chemotherapy is consistent with this observation. The underlying pathophysiology for preterm delivery in this patient group remains unknown, but possible effects of treatments other than radiotherapy cannot be dismissed nor a possible effect of the malignancy being treated. Risk of preterm delivery was also elevated among survivors of Wilms' tumors, a result in agreement with previous findings^{6, 16}, and possibly due to the development of fibrosis after pelvic irradiation which restricts the growth and elastic potential of the uterus³⁰.

Pediatric patients had a high risk of both preterm and early preterm delivery. Most of the increased risk was explained by Wilms' tumor patients. All 25 Wilms tumor patients in our study were diagnosed under the age of 8 years and were most likely pre-pubertal when treated. Pediatric cancer survivors also had an increased risk of delivery earlier than 34 weeks, and there was a non-significant increased risk of LBW infants even after adjustment for duration of pregnancy. However, there was no increase in the risk of delivering an SGA infant, using the internationally accepted definition of SGA³¹.

Results of analyses by treatment were generally in agreement with previous studies^{8, 10, 13, 14}, as risk of preterm delivery was elevated among pediatric and adolescent patients receiving abdomino-pelvic irradiation. In young adults, however, risk of preterm delivery was significantly elevated in patients not receiving radiotherapy. Although previous results on the association of chemotherapy and adverse pregnancy outcomes in pediatric patients are not entirely clear (but generally negative)^{13, 19}, the possibility of a differential effect on the adult reproductive axis or the possible influence of the adult cancers e.g. of the ovary, being treated may explain our finding. As this diagnostic age-group has been overlooked in the past, further studies including information on chemotherapeutic agent and dose administered are needed to confirm this result.

Previous studies have reported significantly elevated risks of preterm delivery and LBW ranging from 1.3–3.6 and 1.3–2.1, respectively (Table 7). Overall our result on preterm delivery among pediatric patients was in agreement with those of previous studies^{8, 10, 13, 14, 19}. Other than chance, several methodological differences may explain small differences in risk estimates. Pediatric patients in the previous studies were aged less than 21 years at diagnosis, whereas our definition of the age group was restricted to patients diagnosed at less than 15 years of age. Comparison groups varied, and majority of studies used the general population^{8, 11, 13}. However, in one study the risks were compared to those patients treated with non-sterilizing surgery¹⁴.

Two studies based on data from the CCSS used siblings as a comparison group and are thus closest in study design^{10, 19}. In the CCSS, recruitment of siblings was based on participation of the survivor, as a random sample of CCSS participants was asked permission to contact their nearest-age full siblings. Furthermore, information on deliveries of both patients and a sample of siblings was self-reported in the form of questionnaires. Our study subjects were identified from population-based national registries, and we had access to information on all patients and siblings, producing a ratio of cancer survivors to siblings of about 1:4 (about

4:1 in the CCSS³²). Our data were then less susceptible to biases associated with participation and response, although births prior to 1987 were excluded. Our data were also not influenced by recall or reporting bias as they were not based on self-reporting; instead information on deliveries was obtained from a nationwide registry which receives data directly from delivery hospitals. Information from national registries allowed reliable access to the important confounders, such as smoking and placental problems, both of which are well established risk factors for preterm delivery^{33, 34}. Although some of these variables (e.g. hypertension) may appear to be in the causal pathway for the outcomes of interest, a significant difference in risks remained in our study even after adjustment.

Familial factors did not explain the observed increase in risk for preterm delivery as even after matching patients with their biological half- and full siblings, the risk of preterm delivery was significantly elevated among former cancer patients.

Socioeconomic position has previously been shown to influence risk of preterm delivery³⁵. In our study results from models adjusting for socioeconomic status did not, however, differ materially from the results of non-adjusted models. Although final models did not adjust for socioeconomic position this cannot be considered to be a substantial source of bias as socioeconomic differences in perinatal health have been shown to be small and are diminishing in Finland³⁶. Other factors not easily accounted for are anxiety and depression, both of which have been associated with increased risk of preterm delivery^{37, 38} and former cancer survivors are known to suffer more psychosocial problems than the general population³⁹. Surveillance bias should also be considered; history of cancer may influence obstetric decisions and may place these individuals under increased surveillance.

In conclusion, our study indicates that women diagnosed with cancer in adolescence and young adulthood as well as in childhood were at increased risk for preterm delivery. Our findings underscore the necessity for continued prenatal follow-up of all former female cancer patients as late as a decade or more after their diagnosis.

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References

1. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, Pastore G, Peris-Bonet R, Stiller CA. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer*. 2009
2. Cvancarova M, Samuelsen SO, Magelssen H, Fossa SD. Reproduction rates after cancer treatment: experience from the Norwegian radium hospital. *J Clin Oncol*. 2009; 27:334–43. [PubMed: 19075285]
3. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD Jr, Lahteenmaki PM. Probability of parenthood after early onset cancer: A population-based study. *International journal of cancer*. 2008; 123:2891–8.
4. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer*. 1999; 86:697–709. [PubMed: 10440699]
5. Byrne J, Rasmussen SA, Steinhorn SC, Connelly RR, Myers MH, Lynch CF, Flannery J, Austin DF, Holmes FF, Holmes GE, Strong LC, Mulvihill JJ. Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. *American journal of human genetics*. 1998; 62:45–52. [PubMed: 9443870]

6. Green DM, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2002; 20:2506–13. [PubMed: 12011129]
7. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Medical and pediatric oncology.* 2002; 38:229–39. [PubMed: 11920786]
8. Reulen RC, Zeegers MP, Wallace WH, Frobisher C, Taylor AJ, Lancashire ER, Winter DL, Hawkins MM. Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:2239–47. [PubMed: 19661083]
9. Stovall M, Donaldson SS, Weathers RE, Robison LL, Mertens AC, Winther JF, Olsen JH, Boice JD Jr. Genetic effects of radiotherapy for childhood cancer: gonadal dose reconstruction. *International journal of radiation oncology, biology, physics.* 2004; 60:542–52.
10. Signorello LB, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, Whitton JA, Green DM, Donaldson SS, Mertens AC, Robison LL, Boice JD Jr. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst.* 2006; 98:1453–61. [PubMed: 17047194]
11. Clark H, Kurinczuk JJ, Lee AJ, Bhattacharya S. Obstetric outcomes in cancer survivors. *Obstetrics and gynecology.* 2007; 110:849–54. [PubMed: 17906019]
12. Magelssen H, Melve KK, Skjaerven R, Fossa SD. Parenthood probability and pregnancy outcome in patients with a cancer diagnosis during adolescence and young adulthood. *Human reproduction (Oxford, England).* 2008; 23:178–86.
13. Mueller BA, Chow EJ, Kamineni A, Daling JR, Fraser A, Wiggins CL, Mineau GP, Hamre MR, Severson RK, Drews-Botsch C. Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. *Archives of pediatrics & adolescent medicine.* 2009; 163:879–86. [PubMed: 19805705]
14. Chiarelli AM, Marrett LD, Darlington GA. Pregnancy outcomes in females after treatment for childhood cancer. *Epidemiology (Cambridge, Mass).* 2000; 11:161–6.
15. Hawkins MM, Smith RA. Pregnancy outcomes in childhood cancer survivors: probable effects of abdominal irradiation. *International journal of cancer.* 1989; 43:399–402.
16. Li FP, Gimbrere K, Gelber RD, Sallan SE, Flamant F, Green DM, Heyn RM, Meadows AT. Outcome of pregnancy in survivors of Wilms' tumor. *Jama.* 1987; 257:216–9. [PubMed: 3025465]
17. Byrne J, Mulvihill JJ, Connelly RR, Austin DA, Holmes GE, Holmes FF, Latourette HB, Meigs JW, Strong LC, Myers MH. Reproductive problems and birth defects in survivors of Wilms' tumor and their relatives. *Medical and pediatric oncology.* 1988; 16:233–40. [PubMed: 2843733]
18. Kalapurakal JA, Peterson S, Peabody EM, Thomas PR, Green DM, D'Angio GJ, Breslow NE. Pregnancy outcomes after abdominal irradiation that included or excluded the pelvis in childhood Wilms tumor survivors: a report from the National Wilms Tumor Study. *International journal of radiation oncology, biology, physics.* 2004; 58:1364–8.
19. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, Pendergrass TW, Robison LL. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *American journal of obstetrics and gynecology.* 2002; 187:1070–80. [PubMed: 12389007]
20. Winther JF, Boice JD Jr, Svendsen AL, Frederiksen K, Stovall M, Olsen JH. Spontaneous abortion in a Danish population-based cohort of childhood cancer survivors. *J Clin Oncol.* 2008; 26:4340–6. [PubMed: 18779621]
21. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland *Acta oncologica (Stockholm, Sweden).* 1994; 33:365–9.
22. Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Medical informatics and the Internet in medicine.* 2002; 27:33–8. [PubMed: 12509121]
23. Pihkala J, Hakala T, Voutilainen P, Raivio K. Characteristic of recent fetal growth curves in Finland. *Duodecim; laaketieteellinen aikakauskirja.* 1989; 105:1540–6.

24. Jakobsson M, Gissler M, Paavonen J, Tapper AM. The incidence of preterm deliveries decreases in Finland. *Bjog*. 2008; 115:38–43. [PubMed: 18053102]
25. Allison, PD. Fixed Effects Regression Models. Newbury Park, CA: Sage; 2009.
26. Green DM, Hall B, Zevon MA. Pregnancy outcome after treatment for acute lymphoblastic leukemia during childhood or adolescence. *Cancer*. 1989; 64:2335–9. [PubMed: 2804924]
27. Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. *Radiother Oncol*. 2004; 73:119–31. [PubMed: 15542158]
28. Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. *Cancer*. 2007; 110:2313–20. [PubMed: 17896787]
29. Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D. Preterm birth, ovarian endometriomata, and assisted reproduction technologies. *Fertility and sterility*. 2009; 91:325–30. [PubMed: 18384780]
30. Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *British journal of obstetrics and gynaecology*. 1999; 106:1265–72. [PubMed: 10609720]
31. Lee PA, Chernauek SD, Hokken-Koelega AC, Czernichow P. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24–October 1, 2001. *Pediatrics*. 2003; 111:1253–61. [PubMed: 12777538]
32. Leisenring WM, Mertens AC, Armstrong GT, Stovall MA, Neglia JP, Lancot JQ, Boice JD Jr, Whitton JA, Yasui Y. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009; 27:2319–27. [PubMed: 19364957]
33. Villalbi JR, Salvador J, Cano-Serral G, Rodriguez-Sanz MC, Borrell C. Maternal smoking, social class and outcomes of pregnancy. *Paediatric and perinatal epidemiology*. 2007; 21:441–7. [PubMed: 17697074]
34. Zlatnik MG, Cheng YW, Norton ME, Thiet MP, Caughey AB. Placenta previa and the risk of preterm delivery. *J Matern Fetal Neonatal Med*. 2007; 20:719–23. [PubMed: 17763272]
35. Morgen CS, Bjork C, Andersen PK, Mortensen LH, Nybo Andersen AM. Socioeconomic position and the risk of preterm birth—a study within the Danish National Birth Cohort. *International journal of epidemiology*. 2008; 37:1109–20. [PubMed: 18577529]
36. Gissler M, Rahkonen O, Arntzen A, Cnattingius S, Nybo Andersen AM, Hemminki E. Trends in Socioeconomic Differences in Finnish Perinatal Health 1991–2006. *Journal of epidemiology and community health*. 2009 In Press.
37. Glynn LM, Schetter CD, Hobel CJ, Sandman CA. Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. *Health Psychol*. 2008; 27:43–51. [PubMed: 18230013]
38. Tanne JH. Women with severe depressive symptoms are twice as likely to have a preterm delivery. *BMJ (Clinical research ed)*. 2008; 337:a2312.
39. Zebrack BJ, Zevon MA, Turk N, Nagarajan R, Whitton J, Robison LL, Zeltzer LK. Psychological distress in long-term survivors of solid tumors diagnosed in childhood: a report from the childhood cancer survivor study. *Pediatric blood & cancer*. 2007; 49:47–51. [PubMed: 16755550]

Figure 1.

Female cancer survivor and female sibling cohorts. Criteria for inclusion of deliveries for both cohorts and numbers of mothers and offspring included in final analyses.

Table 1

Descriptive characteristics of the first post-diagnosis pregnancies of female cancer survivors and first deliveries of female siblings.

Characteristic	No. of live-born children of			
	Patients (N=1309)		Siblings (N=5916)	
		%		%
Age at delivery, years				
<20	32	2.4	393	6.6
20–34	1108	84.6	5057	85.5
>35	169	13.0	466	7.9
Time period of delivery				
1987–1989	135	10.3	1052	17.8
1990–1999	588	44.9	3122	52.8
2000–2006	586	44.8	1742	29.5
Socioeconomic status				
Upper white-collar	222	17.0	686	11.6
Lower white-collar	347	26.5	1626	27.5
Blue-collar	142	10.8	738	12.5
Students	128	9.8	619	10.5
Other*	32	2.4	113	1.9
Missing	438	33.5	2134	36.1
Infant gender				
Male	674	51.5	3019	51.0
Female	635	48.5	2897	49.0
Use of assisted reproductive technology [†]				
Yes	42	3.2	95	1.6
No	1267	96.8	5821	98.4
Maternal smoking of cigarettes				
Yes	175	13.4	1031	17.4
No	1134	86.6	4885	82.6
Maternal high blood pressure				
Yes	88	6.7	265	4.5
No	1221	93.3	5651	95.5
Pre-eclampsia				
Yes	7	0.5	16	0.3
No	1302	99.5	5900	99.7
Placental problems				
Yes	29	2.2	87	1.5
No	1280	97.8	5829	98.5
Maternal infections				
Yes	1	0.1	4	0.1
No	1308	99.9	5912	99.9

Characteristic	No. of live-born children of			
	Patients		Siblings	
	(N=1309)	%	(N=5916)	%
Caesarian sections				
Yes	308	23.5	1081	18.3
No	1001	76.5	4835	81.7
Malpresentation				
Yes	116	8.9	357	6.0
No	1193	91.1	5559	94.0
Maternal diabetes				
Yes	27	2.1	107	1.8
No	1282	97.9	5809	98.2
Duration of pregnancy				
<37wks	102	7.8	298	5.0
37wks or more	1207	92.2	5618	95.0
<34wks	31	2.4	71	1.2
34wks or more	1278	97.6	5845	98.8
Birth weight				
<2500g	80	6.0	221	3.7
2500g or more	1229	94.0	5692	96.2
Missing	0		3	0.1
SGA				
Yes	37	2.8	162	2.7
No	1272	97.2	5751	97.2
Missing	0		3	0.1

* Includes unemployed, housewives, pensioners, women on maternity leave

† In vitro fertilization, intracytoplasmic sperm injection, frozen embryo transfer, insemination, ovum maturation therapy

Table 2
Primary site of cancer by age at diagnosis of women experiencing their first delivery >9months post-diagnosis

Primary site	Diagnostic Age-group					
	Pediatric* Survivors		Adolescent† Survivors		Young Adult‡ Survivors	
	N	%	N	%	N	%
Leukemia	94	31.6	15	6.0	10	1.3
Lymphomas	21	7.1	63	25.3	130	17.0
Hodgkin lymphoma	14		53		87	
Non-Hodgkin lymphoma	7		10		43	
Central nervous system tumours	51	17.2	29	11.6	61	8.0
Sympathetic nervous system tumours	17	5.7	0		3	0.39
Retinoblastoma	12	4.0	0		0	
Kidney	25	8.4	2	0.8	6	0.79
Malignant bone	8	2.7	12	4.8	9	1.2
Soft tissue	18	6.1	20	8.0	59	7.7
Germ-cell	5	1.7	18	7.2	33	4.3
Ovary	3		16		26	
Other germ-cell	2		2		7	
Carcinomas and other malignant epithelial neoplasms	42	14.1	88	35.3	444	58.2
Thyroid	9		41		151	
Cervix	0		1		17	
Breast	1		2		54	
Stomach	0		0		5	
Colon	16		21		50	
Urinary bladder	0		2		1	
Melanoma	7		18		120	
Other carcinomas	9		3		47	
Other	4	1.3	2	0.8	8	1.0
Total	297		249		763	

* Aged 0–14 years at diagnosis

[†] Aged 15–19 years at diagnosis
[‡] Aged 20–34 years at diagnosis

Table 3

Crude and adjusted odds ratios (ORs) for preterm birth, low birth weight and small-for-gestational-age among offspring of women with a history of cancer compared with offspring of female siblings

Birth outcome	Offspring of survivors N=1309 (%)	Offspring of siblings N= 5916 (%)	Crude OR	95% CI [‡]	Adjusted OR [*]	95% CI
Preterm birth (<37wks)	102 (7.8%)	298 (5.0%)	1.59	1.26–2.01	1.46	1.14–1.85
Preterm birth (<34wks)	31 (2.4%)	71 (1.2%)	2.0	1.30–3.06	1.75	1.12–2.72
Low birth weight	80 (6.1%)	221 (3.7%)	1.68	1.29–2.18	1.11 [‡]	0.76–1.64
Small-for-gestational-age	37 (2.8%)	162 (2.7%)	1.03	0.72–1.48	0.89	0.61–1.29

* Adjusted for maternal age, delivery year, child sex, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and cesarean delivery

[‡] Additionally adjusted for gestational weeks

[‡] 95% Confidence interval

Table 4

Risk of preterm birth, low birth weight, and small-for-gestational-age by age of cancer diagnosis of mother, expressed as odds ratios (ORs) comparing offspring of cancer survivors to offspring of female siblings

Birth outcome	Cancer Survivors Age at Diagnosis			Siblings
	0–14 yrs	15–19 yrs	20–34 yrs	
	N=297	N=249	N=763	
Preterm<37wks N	25	19	58	298/5916
Crude OR (95% CI) [‡]	1.73 (1.13–2.65)	1.56 (0.96–2.52)	1.55 (1.16–2.08)	1.00
Adjusted OR* (95% CI)	1.62 (1.05–2.51)	1.56 (0.96–2.55)	1.36 (1.01–1.85)	1.00
Preterm<34wks N	9	5	17	71/5916
Crude OR (95% CI)	2.57 (1.27–5.20)	1.69 (0.68–4.22)	1.88 (1.10–3.20)	1.00
Adjusted OR* (95% CI)	2.38 (1.15–4.94)	1.74 (0.68–4.40)	1.53 (0.87–2.67)	1.00
Low Birth Weight N	21	14	45	221/5913
Crude OR (95% CI)	1.96 (1.23–3.12)	1.53 (0.88–2.67)	1.61 (1.16–2.24)	1.00
Adjusted OR [‡] (95% CI)	1.61 (0.80–3.21)	0.88 (0.38–2.04)	1.03 (0.63–1.67)	1.00
Small-for-gestational-age N	7	9	21	162/5913
Crude OR (95% CI)	0.86 (0.40–1.84)	1.33 (0.67–2.64)	1.00 (0.63–1.59)	1.00
Adjusted OR* (95% CI)	0.70 (0.32–1.52)	1.18 (0.59–2.37)	0.87 (0.54–1.41)	1.00

* Adjusted for maternal age, delivery year, child gender, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and cesarean delivery

[‡] Additionally adjusted for gestational weeks

[‡] 95% Confidence interval

Risk of preterm delivery and low birth weight by cancer diagnostic age-group and time from diagnosis to delivery. Adjusted odds ratios (ORs) only.

Table 5

Birth outcome	Age at Cancer Diagnosis						Sibs
	Pediatric (0–14)		Adolescent (15–19)		Adult (20–34)		
	Delivery<10yr	Delivery≥10yr	Delivery<10yr	Delivery≥10yr	Delivery<10yr	Delivery≥10yr	
Preterm delivery <37weeks N1/N	3/54	22/243	12/176	7/73	48/705	10/58	298/5916
OR* (95% CI) [‡]	1.11 (0.34–3.64)	1.73 (1.08–2.75)	1.46 (0.80–2.67)	1.78 (0.79–3.98)	1.26 (0.91–1.74)	2.66 (1.26–5.63)	
Early Preterm delivery <34weeks N1/N	1/54	8/243	3/176	2/73	16/705	1/58	71/5916
OR* (95% CI)	1.81 (0.24–13.93)	2.48 (1.15–5.36)	1.58 (0.49–5.17)	2.04 (0.48–8.76)	1.63 (0.92–2.88)	0.72 (0.09–5.62)	
Low Birth Weight N1/N	2/54	19/243	9/176	5/73	36/705	9/58	221/5913
OR [‡] (95% CI)	0.89 (0.11–7.35)	1.74 (0.84–3.62)	0.97 (0.36–2.56)	0.68 (0.14–3.30)	0.91 (0.53–1.55)	2.05 (0.70–6.05)	

* Adjusted for maternal age, delivery year, child gender, maternal smoking, maternal hypertension, placental problems, use of assisted reproductive technologies, malpresentation and cesarean delivery

[†] Additionally adjusted for gestational weeks

[‡] 95% Confidence interval

N1 number of adverse outcomes

Table 6

Risk of preterm delivery by cancer site among 1309 female survivors of cancer with respect to the siblings comparison group

Primary site	Preterm Delivery			
	<37wks		<34wks	
	Patients	OR (95%CI)	Patients	OR (95%CI)
	N1/N		N1/N	
Leukemia	9/119	1.47 (0.73–2.96)	2/119	1.32 (0.31–5.60)
Lymphomas	16/214	1.38 (0.80–2.36)	3/214	1.04 (0.32–3.41)
Brain and CNS	10/141	1.33 (0.69–2.59)	5/141	2.67 (1.04–6.87)
Sympathetic nervous system	2/20	2.19 (0.50–9.70)	1/20	4.30 (0.53–34.93)
Retinoblastoma	1/12	1.80 (0.23–14.30)	0/12	NA
Kidney	8/33	5.50 (2.39–12.64)	4/33	9.31 (2.93–29.57)
Malignant bone	2/29	0.99 (0.22–4.37)	0/29	NA
Soft tissue sarcomas	6/97	1.15 (0.49–2.69)	0/97	NA
Germ cell	9/56	2.94 (1.38–6.25)	3/56	3.26 (0.91–11.69)
Carcinomas	38/574	1.22 (0.86–1.76)	13/574	1.68 (0.90–3.11)
Other	1/14	1.52 (0.20–11.82)	0/14	NA

N1 denotes the number of preterm deliveries

N denotes the denominator of mothers diagnosed with the particular primary site of interest

NA denotes non applicable

Table 7
Summary of recent studies on preterm birth and low birth weight (LBW) among children of female cancer survivors

Authors & year	Age at cancer diagnosis	Treatment period	Comparison group	Patients N	Pregnancies N	Outcome Determination	Preterm OR (95% CI)	LBW OR (95% CI)	Comments
Mueller et al. ¹² 2009	0–19	1973–2000	General population	1898	1898	Registry linkage	1.54 (1.30–1.83)	1.31 (1.10–1.57)	Migration in or out of reporting area not known
Reulen et al. ¹³ 2009	0–15	1940–1991	General population	1991	4113	Questionnaire	3.2 (2.1–4.7) *	1.9 (1.1–3.2) *	Only pediatric patients
Clark et al. ¹⁰ 2007	0–43	1980–2005	General population	917	1 122	Registry linkage	1.33 (1.01–1.76)	1.03 (0.77–1.37)	No diagnostic-age specific risk estimates
Signorello et al. ⁹ 2006	0–20	1970–1986	Sample of female siblings	1264	3529	Questionnaire	1.9 (1.4–2.4)	1.3 (0.9–1.9)	Non-random selection of comparison group
Green et al. ¹⁹ 2002	0–20	1970–1986	Sample of female siblings	1915	4029	Questionnaire	NA	2.05 (1.42–2.95)	No adjustment for gestational age
Chiarelli et al. ¹⁸ 2000	0–19	1964–1988	Patients treated with non-sterilising surgery only	340	340	Questionnaire	3.64 (1.33–9.96)	3.29 (0.97–11.1)	Only pediatric patients

* Among female cancer survivors treated with abdominal radiotherapy.