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Birth outcomes among offspring of adult cancer survivors: A population-based study

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Do cancer and cancer treatment influence patients' subsequent pregnancies and outcomes for the offspring? In this study, we compared birth outcomes in 3,915 female and male survivors and 144,653 controls from the general population with similar parity, by merging data from the Cancer Registry and the Medical Birth Registry of Norway. The cancer survivors were diagnosed at age 16–45 in the period 1967–2004. Subgroups of nulliparous survivors (childless before cancer) and primiparous (one pregnancy before and one after cancer) were analyzed, using logistic regression to compare birth outcomes with controls, focusing perinatal death, congenital anomalies, preterm birth (<37 gestational weeks) and low birth weight (LBW, <2,500 g). We adjusted for maternal age, birth period and educational level. Nulliparous female survivors' offspring had increased risk of preterm birth (OR = 1.30 [95% CI 1.05–1.61]) but similar risks of LBW and perinatal death as their controls. Primiparous female survivors differed from their controls, with higher frequency of preterm birth (OR = 1.89 [95% CI 1.40–2.56]) and LBW at term (OR = 2.02 [95% CI 1.15–3.55]). A borderline significant increase of perinatal death was seen among offspring of primiparous female survivors, with OR = 1.92 (95% CI 0.98–3.76). Offspring of male survivors did not differ from their controls. For all cancer types combined, no increased risk of congenital anomalies was seen among either female or male survivors' offspring. Pregnant female cancer survivors should be offered close follow-up, as there is an increased risk of adverse birth outcomes, in particular among those with higher parities.

An increasing number of adult cancer survivors are having children after cancer, and the survivors are concerned about their offspring's health.[1,2] Theoretically, cancer treatment might cause adverse birth outcomes like congenital anomalies.

Several papers have been published about birth outcomes among childhood cancer survivors.[3–9] Preterm birth (before 37 gestational weeks) and low birth weight (LBW; below 2,500 g) are common findings among the offspring of female childhood cancer survivors who received abdominal, pelvic or total body irradiation.[3,6] Regarding adult cancer survivors, the literature is more scarce and with inconsistent results. Increased risks of preterm birth, LBW, perinatal death and congenital anomalies are reported in several studies concerning offspring of female survivors,[9–12] while other authors did not find any differences compared to controls.[7,8,13–15] The outcomes for offspring of male cancer survivors are reassuring,[4,5,7] except for two recent publications reporting increased risk of congenital anomalies.[10,16]

In this population-based study, we compared birth outcomes among cancer survivors and a control group from the general population, all in the age group 16–45 years. Our main objective was to follow up on results recently reported by Magelssen *et al.*[10] based on a material from the Norwegian Radium Hospital, concluding that preterm birth, LBW and perinatal deaths were more frequent among offspring of female survivors than controls from the general population. As the risks of outcomes like perinatal death and preterm birth are closely linked to birth order,[17] we wanted to see if parity had an additional effect for cancer survivors, and analyzed nulli- and primiparous separately. Further, we wanted to assess whether the risk of congenital anomalies in male cancer survivors' offspring is higher than that of the general population, also reported by Magelssen *et al.* and in a recent population-based study from Denmark and Sweden.[10,16]

Key words: cancer survivor, pregnancy, birth outcome

Abbreviations: CI: confidence interval; CRN: Cancer Registry of Norway; ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilization; LBW: low birth weight; MBRN: Medical Birth Registry of Norway; SGA: small for gestational age

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What's new?

As more adults survive cancer and subsequently have children, more people are asking how the disease and its treatment impact those children. This study compared birth outcomes among male and female cancer survivors with those of a control group. They looked at preterm birth, low birth weight and other factors, and also segregated the data depending on whether the woman had a child before developing cancer, or whether the post-diagnosis child was her first. They found an increased risk of preterm birth for all female survivors, and increased risk of low birth weight, caesarian section, and pre-eclampsia in only the women who had a prior child. No significant differences were found among the offspring of male survivors.

Material and Methods

Data sources

Based on compulsory notification, the Cancer Registry of Norway (CRN) contains information on all cancer cases occurring in Norway from 1953 onwards.[18] Cancer type, date of diagnosis, extent or stage of disease at diagnosis and initial treatment in broad terms are recorded. In general, extent of disease of solid tumors is classified as localized, regional spread, distant spread, or of unknown extent. Brain tumors and nonsolid tumors are not classified by stage or extent.[19,20]

The Medical Birth Registry of Norway (MBRN) was established in 1967 and contains information on pregnancies lasting at least 16 weeks, with compulsory notification by the midwives or physicians attending the birth. The MBRN provides information on demographic data of the parents, their previous reproductive history, maternal health before and during pregnancy, delivery complications, birth outcomes, including anthropometric measurements and any diagnoses of the infant made during the stay at the obstetric clinic. Gestational age is based on last menstrual date, and since 1999, also on ultrasound estimation. As 1988, information on the use of *in vitro* fertilization (IVF), including intracytoplasmic sperm injection (ICSI), is reported.[21,22] In the following, we will use the words "birth" or "pregnancy" interchangeably for births and pregnancies where outcomes are registered in the MBRN.

Statistics Norway provides statistics on the Norwegian population. For this study, vital status as of December 31, 2006 and date of death or emigration were recorded, as well as parental educational level at the time of inclusion.[23]

Construction and selection of study population

With approval from the National Data Inspectorate and the Regional Committee for Medical Research Ethics, data from the three above sources were linked by means of the personal identification number given to all Norwegian inhabitants.

A total of 53,835 individuals were registered in the CRN with an invasive cancer diagnosed at the age of 16–45 years during 1967–2004. All malignant neoplasms and all intracerebral tumors according to the International Classification of Disease version 7 (ICD-7 140–207) were included, except basal cell carcinomas.

All cancer survivors with at least one singleton pregnancy registered after cancer in the period 1967–2006 were identified for this study ($n = 5{,}004$). The original data selection included all survivors, and a control group from the general population made up of five age- and sex-matched controls per survivor.[2] In this study, the matching of the original data selection was broken, and only controls with at least one singleton pregnancy registered in the period 1967–2006, were used ($n = 144{,}653$, Fig. 1).

To disentangle cancer effects on birth outcomes from parity effects, we studied birth outcomes after cancer by identifying survivors with either no previous (nulliparous) or one previous (primiparous) pregnancy at the time of cancer diagnosis. Thus nulliparous survivors ($n = 2{,}574$) had their first birth after cancer, and primiparous survivors ($n = 1{,}341$) had one birth before and (at least) one birth after cancer. Further, we analyzed birth outcomes for the most frequent cancer types among adolescents and young adults. Each birth was linked to the respective parent by means of the personal identification number, providing sibling files where the mother or father was the unit of analysis. For comparison, we used all nulliparous and primiparous controls, with at least one or two births, respectively.

We defined births after cancer as all births where the last menstrual period coincided with or was after the date of diagnosis. When menstrual dates were missing [$N = 7{,}363$ (4.9%)], the pregnancy duration based on ultrasound estimations was used to categorize the pregnancy as initiated before or after the cancer diagnosis. Pregnancies shorter than 22 weeks of gestation, or with infants less than 500 g, were defined as spontaneous abortions and excluded.

The following outcomes were studied with dichotomized variables for all cancer types seen together and for each of the most frequent cancer types: perinatal death (stillbirth from 22 weeks or death $\leq$7 days of life), preterm and very preterm birth ($<$37 and $<$32 completed gestational weeks, respectively), low birth weight (LBW; $<$2,500 g), low Apgar score at 5 min (below 7) and major congenital anomalies according to EUROCAT.[24] Subanalyses including cancer survivors giving birth within 2 years were also performed for the above listed outcomes. We also evaluated the use of IVF/ICSI, registered pre-eclampsia, and delivery by caesarian section. Mean birth weight was assessed for offspring of all cancer types seen together, as well as in a subgroup without malignant melanoma survivors, to simulate the selection used in the hospital-based study by Magelssen *et al.*[10]

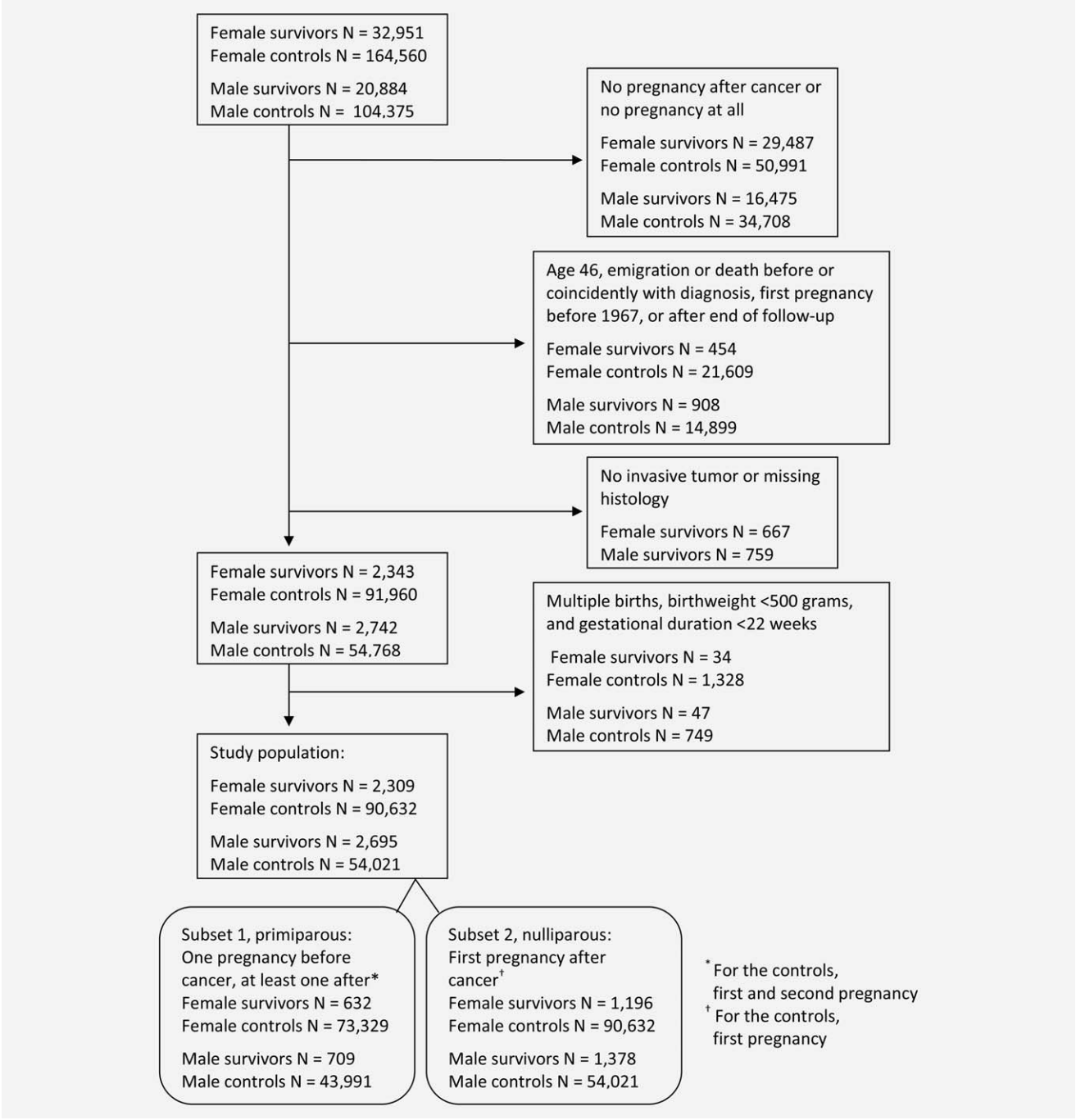

Figure 1. Heading: Cohort selection. Footnote: Flow chart showing the exclusion of survivors and controls not eligible for this study. Initially, all cancer patients diagnosed at age 16–45-years-old, from 1967 to 2004, were identified, with five controls matched by age and sex.

Epidemiology

Statistical analyses

Standard descriptive methods with counts and proportions for categorical data, and mean and standard deviations for continuous data were applied, using SPSS. Odds ratio (OR) with 95% confidence intervals (CI) as obtained from standard contingency tables or logistic regression, were used to compare birth outcomes between cases and controls. When analyzing preterm birth, misclassifications of gestational age were removed on the basis of current birth weight by gestational age standards, excluding z-scores larger than 4[25]. Adjustments were made for birth period (1967–1975, thereafter 5-years intervals), maternal age (<20 years, 20–24, 25–29, 30–34 and 35+ years) and educational level, which was categorized based on total duration, low (≤9 years), medium (10–14 years), high (≥15 years), or unknown. To assess adjusted mean birth weight, we used univariate ANOVA. P-values <0.05 were considered statistically significant, and all tests were two-sided.

Table 1. Background characteristics for the survivor and control cohorts

	Female survivors		Female controls		Male survivors		Male controls	
	Nulliparous	Primiparous	Nulliparous	Primiparous	Nulliparous	Primiparous	Nulliparous	Primiparous
Number	1,196	632	90,632	73,329	1,378	709	54,021	43,991
Age at diagnosis, mean (SD)	24.0 (5.1)	27.3 (4.5)			25.1 (5.0)	28.9 (5.0)		
Age at birth, mean (SD)	29.1 (4.9)	31.1 (4.4)	24.6 (4.9)	27.6 (4.6)	30.7 (4.9)	32.7 (5.0)	27.0 (5.0)	30.2 (4.9)
Time diagnosis–birth, mean (SD)	5.1 (3.5)	3.8 (2.8)			5.7 (4.0)	3.7 (3.0)		
Parity, no. (%)								
0	452 (38)		15,930 (18)		492 (36)		8,819 (16)	
1	532 (44)	469 (74)	42,544 (47)		629 (45)	448 (63)	24,781 (46)	
2+	212 (18)	163 (26)	32,158 (35)		257 (19)	261 (37)	20,421 (38)	
Maternal age, no. (%)								
<20 years	9 (1)	0	12,680 (14)	1,124 (2)	44 (3)	2 (1)	7,640 (14)	860 (2)
20–24 years	201 (17)	33 (5)	36,999 (41)	19,027 (26)	326 (24)	79 (11)	22,555 (42)	11,781 (27)
25–29 years	468 (39)	213 (34)	26,965 (30)	29,715 (41)	557 (40)	281 (39)	16,810 (31)	18,210 (41)
30–34 years	348(29)	248 (39)	10,289 (11)	17,421 (24)	335 (24)	257 (36)	5,626 (10)	10,383 (24)
≥35 years	170 (14)	138 (22)	3,699 (4)	6,042 (8)	116 (8)	90 (13)	1,390 (3)	2,757 (6)
Birth period, no. (%)								
1967–1985	261 (22)	141 (22)	62,925 (69)	43,812 (60)	290 (21)	181 (25)	32,303 (60)	22,550 (51)
1986–1995	357 (30)	205 (33)	19,756 (22)	20,250 (28)	388 (28)	197 (28)	13,893 (26)	12,959 (29)
1996–2006	578 (48)	286 (45)	7,951 (9)	9,267 (13)	700 (51)	331 (47)	7,825 (14)	8,482 (19)
Educational level, no. (%)								
Low (≤9 years)	268 (22)	118 (19)	17,321 (19)	13,932 (19)	303 (22)	119 (17)	8,884 (16)	6,821 (16)
Medium (10–14 years)	450 (38)	253 (40)	27,853 (31)	22,768 (31)	540 (39)	269 (38)	16,740 (31)	13,656 (31)
High ≥15 years	308 (26)	165 (26)	16,038 (18)	12,920 (18)	301 (22)	165 (23)	8,227 (15)	6,790 (15)
Unknown	170 (14)	96 (15)	29,420 (32)	23,709 (32)	234 (17)	156 (22)	20,170 (37)	16,724 (38)
Type of cancer, no. (%)								
Breast cancer	58 (5)	43 (7)						
Cervical cancer	76 (6)	59 (9)						
Ovarian cancer	44 (4)	21 (3)						
Testicular cancer					531 (39)	274 (39)		
Malignant melanoma	394 (33)	232 (37)			219 (16)	128 (18)		
Brain tumors	135 (11)	42 (7)			131 (10)	69 (10)		
Thyroid cancer	151 (13)	99 (16)			49 (4)	23 (3)		

Table 1. Background characteristics for the survivor and control cohorts (Continued)

	Female survivors		Female controls		Male survivors		Male controls	
	Nulliparous	Primiparous	Nulliparous	Primiparous	Nulliparous	Primiparous	Nulliparous	Primiparous
Hodgkin lymphoma	120 (10)	39 (6)			162 (12)	66 (9)		
Non-Hodgkin lymphoma	42 (4)	17 (3)			67 (5)	31 (4)		
Leukemia	22 (2)	4 (1)			37 (3)	12 (2)		
Others	154 (13)	76 (12)			182 (13)	105 (15)		

The survivors have at least one pregnancy after cancer, nulliparous reflects those who have their first pregnancy ever after cancer, and primiparous reflects those who have one pregnancy before and at least one after cancer. Only singleton pregnancies are included. Age at birth reflects the parental age for each gender (maternal age at the respective pregnancy for females and analogous for males). Only maternal age for the current birth are adjusted for in the multivariate analyses in the following. Parity reflects the total number of children, born both before and after the cancer diagnosis for the survivors.

Results

The study population included 3,915 female and male survivors who had at least one singleton birth after cancer and for comparison, 144,653 controls (Fig. 1). Malignant melanoma and thyroid cancer were the most frequent cancer types among female survivors, whereas testicular cancer and malignant melanoma were the two most frequent malignancies among males. Parental age at birth was higher among survivors of both genders than controls (Table 1).

First pregnancy after cancer (Nulliparous, n = 2,574)

Female survivors had increased risk of preterm delivery compared to controls (adjusted OR = 1.30 [95% CI 1.05–1.61]), and a borderline increased risk of LBW, adjusted OR = 1.26 ([95% CI 0.99–1.60], Table 2). The increased risk of LBW disappeared when restricting the analyses to term infants. There was a weak, but nonsignificant effect on very preterm birth among female survivors (adjusted OR =1.32 [0.79–2.20]), and no significant effects on Apgar score, use of IVF/ICSI, caesarian section, or occurrence of pre-eclampsia. Crude and adjusted mean birth weights were similar for infants of survivors and controls (Table 2).

We could not demonstrate any increased risk of adverse outcomes among the offspring of male survivors relative to their controls. The only difference between male survivors and controls, was the increased use of IVF/ICSI among survivors (adjusted OR = 1.83 [95% CI 1.35–2.49], Table 2).

There were no differences between survivors and controls regarding offspring perinatal death or congenital anomalies, even when restricting to analyses of survivors giving birth within 2 years (data not shown), or for the subgroup where malignant melanoma was excluded (data not shown). However, in subanalyses of selected cancer types, we found an increased risk of congenital anomalies among the offspring of ovarian cancer survivors, (4/44 pregnancies, adjusted OR = 3.23 [95% CI 1.15–9.09], Supporting Information Table).

One pregnancy before cancer, at least one after (Primiparous, n = 1,385)

For the birth before cancer diagnosis, we could not demonstrate any significant differences in birth outcomes between cancer survivors and controls. This applied to both genders (Table 3). However, the use of IVF/ICSI was significantly increased among female survivors relative to controls, and with a nonsignificantly increased estimate for male survivors.

When looking at the birth after cancer, female survivors had higher risk of preterm birth (OR = 1.89; 1.40–2.56), and a three times higher risk of very preterm birth than controls. The risk of LBW was doubled among female survivors' offspring, also when preterm babies were excluded. Pre-eclampsia and delivery by caesarian section were also more frequent. Female survivors experienced a close to

Table 2. Nulliparous: Effects on birth outcomes to nulliparous female and male cancer survivors compared to their controls

Outcomes	Female survivors *n*/Total	Female controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)	Male survivors *n*/Total	Male controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)
Perinatal mortality	9/1,196	1,169/90,632	0.58 (0.30–1.12)	0.91 (0.47–1.78)	9/1,378	544/54,021	0.69 (0.35–1.33)	1.10 (0.56–2.15)
Preterm delivery	100/1,189	4,940/85,720	1.50 (1.22–1.85)	1.30 (1.05–1.61)	73/1,364	2,780/51,119	0.98 (0.77–1.25)	0.92 (0.72–1.18)
Very preterm delivery	16/1,189	802/85,720	1.44 (0.88–2.38)	1.32 (0.79-2.20)	6/1,364	406/51,119	0.55 (0.25-1.24)	0.54 (0.24-1.22)
Low birth weight (LBW)	77/1,196	4,448/90,632	1.33 (1.06–1.68)	1.26 (0.99–1.60)	52/1,378	2,439/54,021	0.83 (0.63–1.10)	0.80 (0.61–1.07)
LBW, term infants	28/1,095	1,948/85,461	1.13 (0.77–1.64)	1.17 (0.80–1.73)	21/1,300	1,087/51,126	0.76 (0.49–1.17)	0.78 (0.50–1.21)
Apgar <7 (5 min)	16/1,074	745/49,198	0.98 (0.60–1.62)	0.82 (0.50–1.37)	24/1,249	436/33,429	1.48 (0.98–2.25)	1.31 (0.86–1.99)
Congenital anomalies	37/1,196	2,324/90,632	1.21 (0.87–1.69)	0.99 (0.71–1.38)	38/1,378	1,357/54,021	1.08 (0.78–1.51)	0.92 (0.66–1.29)
IVF/ICSI	24/876	443/22,748	1.42 (0.94–2.15)	0.88 (0.58–1.36)	54/1,032	339/18,570	2.97 (2.21–3.99)	1.83 (1.35–2.49)
Caesarean section	201/1,196	8,186/90,632	2.04 (1.75–2.37)	1.01 (0.86–1.18)	221/1,378	5,207/54,021	1.79 (1.55–2.07)	1.07 (0.92–1.25)
Pre-eclampsia	65/1,196	3,585/90,632	1.40 (1.08–1.80)	1.03 (0.80–1.33)	80/1,378	2,134/54,021	1.50 (1.19–1.89)	1.22 (0.96–1.54)

Nulliparous meaning no previous births at the time of cancer diagnosis. Only singleton pregnancies with gestational age ≥22 weeks or birth weight ≥500g were included. Adjustments: maternal age, period of birth, maternal or paternal education, respectively. For definitions of the outcomes, see Methods; Construction and selection of study population.

doubled risk of perinatal deaths, of borderline significance, while the risk of congenital anomalies did not significantly differ between the offspring of survivors and controls (Table 3). When restricting analyses to female survivors who gave birth within 2 years after diagnosis, the effect on perinatal death was further elevated (4/169 pregnancies, adjusted OR = 3.12; 1.15–8.49), with no difference for any other outcome. For the male survivors, the only effect after cancer was seen for the use of IVF/ICSI, which was significantly increased (Table 3). For male survivors' offspring, the results were basically similar to those of the controls also when restricting analyses to births within 2 years after diagnosis.

Mean birth weights (with 95% CI) are shown in Figure 2 for first and second births. We could not demonstrate any significant differences between survivors and controls in the total material (A). However, we observed a significant lower increase in mean birth weight from first to second birth among female cancer survivors when excluding malignant melanoma (B), with a mean increase of 37 grams among cancer survivors compared to 146 grams among the controls. The resulting mean birth weight for second infants was therefore significantly lower for infants of cancer survivors.

For selected subtypes of cancer, increased risk of congenital anomalies was seen among the offspring of breast cancer survivors (4/43 pregnancies, OR = 3.49 (95% CI 1.24–9.82), Fig. 3, Supporting Information Table). Further, females surviving cervical and ovarian cancer were those with the highest risk of preterm delivery and offspring with LBW in general, while breast and cervical cancer was associated with increased risk of LBW at term (Fig. 3).

Discussion

In this population-based study with 3,915 female and male cancer survivors having children after cancer, we found increased risk of preterm birth in all female survivors, with OR = 1.30; 1.05–1.61) for nulliparous and OR=1.89; 1.40–2.56) for primiparous and survivors. Increased risks of LBW babies, pre-eclampsia and delivery by caesarean section were only seen in pregnancies after cancer treatment for the primiparous female survivors. The risks of perinatal death and low Apgar score after 5 min did not significantly differ among infants of mothers with a history of cancer than those without. Among the male survivors, no differences from controls were seen for any outcomes except that survivors more frequently used IVF/ICSI. For all cancer types combined, and separately for male and female survivors, no higher risk of congenital anomalies among offspring born by survivors than controls was demonstrated.

Among the limitations of this study are the lack of individual, detailed treatment data and information about physical condition among the offspring after the first days of life. Also, even though the whole population of cancer survivors during a period of almost 40 years was included,

Table 3. Primiparous: Effects on birth outcomes for first and second pregnancies to cancer survivors who had their second pregnancy after cancer, compared to controls with similar parities

	First pregnancy, before cancer				Second pregnancy, after cancer			
Outcomes	Female survivors *n*/Total	Female controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)	Female survivors *n*/Total	Female controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)
Females'offspring								
Perinatal mortality	8/662	1,053/74,279	0.85 (0.42–1.71)	1.18 (0.58–2.38)	9/632	715/73,329	1.47 (0.76–2.85)	1.92 (0.98–3.76)
Preterm delivery	35/581	3,803/70,422	1.12 (0.80–1.58)	1.08 (0.77–1.53)	48/623	2,844/68,874	1.94 (1.44–2.61)	1.89 (1.40–2.56)
Very preterm delivery	2/581	628/70,422	0.38 (0.10-1.54)	0.41 (0.10-1.65)	12/623	472/68,874	2.85 (1.60-5.08)	3.01 (1.67-5.43)
Low birth weight (LBW)	32/662	3,398/74,279	1.06 (0.74–1.51)	1.10 (0.77–1.57)	43/631	2,161/73,241	2.41 (1.76–3.29)	2.31 (1.68–3.18)
LBW, term infants	13/625	1,503/70,292	0.97 (0.56–1.69)	1.05 (0.60–1.82)	13/578	696/66,146	2.16 (1.24–3.77)	2.02 (1.15–3.55)
Congenital anomalies	20/662	1,850/74,279	1.22 (0.78–1.91)	1.09 (0.69–1.70)	19/632	1,597/73,329	1.39 (0.88–2.20)	1.14 (0.72–1.82)
Apgar <7 (5 min)	8/553	574/38,615	1.01 (0.50–2.04)	1.00 (0.50–2.03)	5/574	471/48,657	0.90 (0.37–2.18)	0.77 (0.32–1.88)
IVF/ICSI	10/350	178/16,416	2.68 (1.41–5.12)	2.85 (1.46–5.56)	5/466	203/24,877	1.32 (0.54–3.22)	0.85 (0.34–2.08)
Caesarean section	84/662	5,691/74,279	1.75 (1.39–2.21)	1.20 (0.94–1.51)	124/632	5,767/73,329	2.86 (2.35–3.49)	1.75 (1.43–2.15)
Pre-eclampsia	33/662	2,768/74,279	1.36 (0.95–1.93)	1.15 (0.81–1.64)	24/632	1,329/73,329	2.14 (1.42–3.23)	1.58 (1.04–2.39)
	Male survivors *n*/Total	Male controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)	Male survivors *n*/Total	Male controls *n*/Total	Crude OR (95% CI)	Adjusted OR (95% CI)
Males'offspring								
Perinatal mortality	3/723	470/44,511	0.39 (0.13–1.22)	0.49 (0.16–1.52)	4/709	328/43,991	0.76 (0.28–2.03)	1.05 (0.39–2.84)
Preterm delivery	28/631	2,183/42,187	0.85 (0.58–1.25)	0.84 (0.58–1.24)	25/705	1,644/41,216	0.89 (0.59–1.32)	0.90 (0.60–1.34)
Very preterm delivery	3/631	318/42,187	0.63 (0.20-1.97)	0.66 (0.21-2.07)	3/705	248/41,216	0.71 (0.23-2.21)	0.79 (0.25-2.50)
Low birth weight (LBW)	26/723	1,901/44,511	0.84 (0.56–1.24)	0.87 (0.59–1.29)	23/709	1,209/43,991	1.19 (0.78–1.81)	1.31 (0.86–2.00)
LBW, term infants	17/695	842/42,241	1.23 (0.76–2.00)	1.30 (0.80–2.12)	11/681	482/42,253	1.42 (0.78–2.60)	1.64 (0.89–3.01)
Congenital anomalies	20/723	1,098/44,511	1.13 (0.72–1.76)	1.02 (0.65–1.59)	18/709	981/43,991	1.14 (0.71–1.83)	1.03 (0.64–1.66)
Apgar <7 (5 min)	6/571	330/26,466	0.84 (0.37–1.89)	0.79 (0.35–1.78)	6/630	282/31,610	1.07 (0.47–2.41)	1.04 (0.46–2.36)
IVF/ICSI	8/387	152/13,720	1.88 (0.92–3.86)	1.90 (0.91–3.97)	23/497	155/18,822	5.84 (3.74–9.14)	4.01 (2.53–6.35)
Caesarean section	73/723	3,758/44,511	1.22 (0.95–1.56)	0.97 (0.76–1.25)	74/709	3,613/43,991	1.30 (1.02–1.66)	0.95 (0.74–1.22)
Pre-eclampsia	24/723	1,685/44,511	0.87 (0.58–1.32)	0.79 (0.52–1.19)	19/709	870/43,991	1.37 (0.86–2.16)	1.14 (0.71–1.81)

Only singleton pregnancies with gestational age ≥22 weeks or birth weight ≥500g were included. Adjustments: maternal age, period of birth, maternal or paternal education, respectively. For definitions of outcomes, see Methods; Construction and selection of study population.

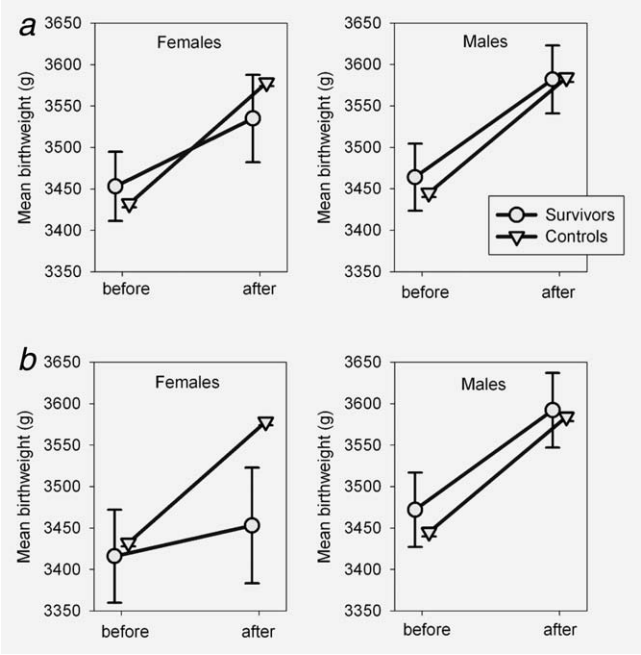

Figure 2. Heading: Mean birth weight of first and second births for primiparous. Footnote: Mean birth weight (crude, with 95% CI) for the offspring of primiparous cancer survivors and controls. "Before" and "after" refers to the first and second pregnancy, for cancer survivors the pregnancies before and after diagnosis. A: Total material; B: Malignant melanoma survivors omitted.

postcancer pregnancy was a relatively rare event when splitting into different cancer types. Thus, the numbers regarding adverse outcomes were small in these analyses, and some findings might be due to chance.

Offspring of female survivors had higher risks of preterm birth after cancer. Preterm birth was most frequently seen after ovarian and cervical cancer, and brain tumors. For brain tumors, hormonal alterations and maternal morbidity, including medication, could be factors explaining the higher risk of preterm delivery. Similar results are reported in a study covering both childhood and adulthood cancer.[9] Treatment of gynecological cancer might result in side-effects like fibrotic changes and adverse effects on the vascular bed of the uterus caused by surgery or irradiation.[12] Cervical cancer survivors have a shorter cervix after trachelectomy or conization, which increases the risk of preterm birth and also the risk of infections, another risk factor for very preterm birth.[12]

LBW is an imperfect measure of growth restriction, as it may be the result of both preterm delivery and impaired growth. We therefore performed subanalyses restricted to those born at term to avoid LBW caused by shorter gestations. Also, we analyzed small for gestational age (SGA), but did not find any differences among the groups, most likely because the LBW/preterm infants in general were not severely enough growth restricted to meet the SGA criteria. When excluding preterm infants, only primiparous cancer survivors' offspring had significantly increased risk of LBW. Stratified on cancer types, the risk of LBW was seen for breast and cervical cancer survivors' offspring. Regarding breast cancer, this finding is in line with some studies, but not all.[11,13] Delivery by caesarian section was frequently used among primiparous survivors of all cancer types, and might be a factor influencing the prevalence of LBW and preterm delivery. Caesarean section deliveries might be indicated for gynecological cancer survivors, but in general probably chosen because of existing or expected maternal morbidity.

It is reassuring that no significantly increased risk of the most severe birth outcomes, perinatal death and congenital anomalies, were seen when all cancer types were combined. There was, however, an almost doubled risk of perinatal deaths among primiparous females, though of borderline significance. This risk was significantly increased when female survivors delivered within 2 years after diagnosis.

The increased risk of congenital anomalies among primiparous breast and nulliparous ovarian cancer survivors' offspring might be chance findings since the numbers were small, and seen in different parity groups. Regarding breast cancer, similar results were observed in a Swedish population-based material, with increased risk for the period 1973–2002, but highest for the last part, 1988–2002, OR = 2.1 (95% CI 1.2–3.7).[11] Possible explanations might be the cytotoxic effects mediated by more intensive chemotherapy, which has increased during recent decades. Other similar publications did not report any adverse birth outcomes among the offspring of breast cancer survivors.[13,26–28]

Regarding risk of congenital anomalies, both the Norwegian hospital-based study by Magelssen *et al.*[10] and the cohort study based on Swedish and Danish registers by Ståhl *et al.*,[16] reported a higher risk for the offspring of male survivors compared with the general population. All anomalies, also minor, were included in the Norwegian study, while our study only assessed major congenital anomalies. Further, there might be a selection of patients referred to a tertiary referral cancer centre as the Norwegian Radium Hospital, which could include proportionally more patients with severe disease, in need of more intensive treatment and hence stronger adverse effect on the gonadal function. Finally, in the Norwegian study, the elevated anomaly risk was only seen for the males childless at diagnosis, not for those already having one child before diagnosis.[10] Ståhl *et al.* found elevated risk of anomalies among male survivors' offspring assessed among all pregnancies after cancer, regardless of parity, but higher among childhood cancer survivors than those diagnosed in adulthood. The cancer types associated with increased risk of anomalies were those affecting skin, eye and the central nervous system, a pattern difficult to explain.[16]

The finding that IVF/ICSI was more common among male cancer survivors was not surprising, and the low estimates for female survivors were also expected, as females have fewer possibilities of fertility-preserving attempts before treatment than males. IVF/ICSI was more frequently used before diagnosis for female survivors, which could reflect a common etiology for reduced fertility and risk of cancer.

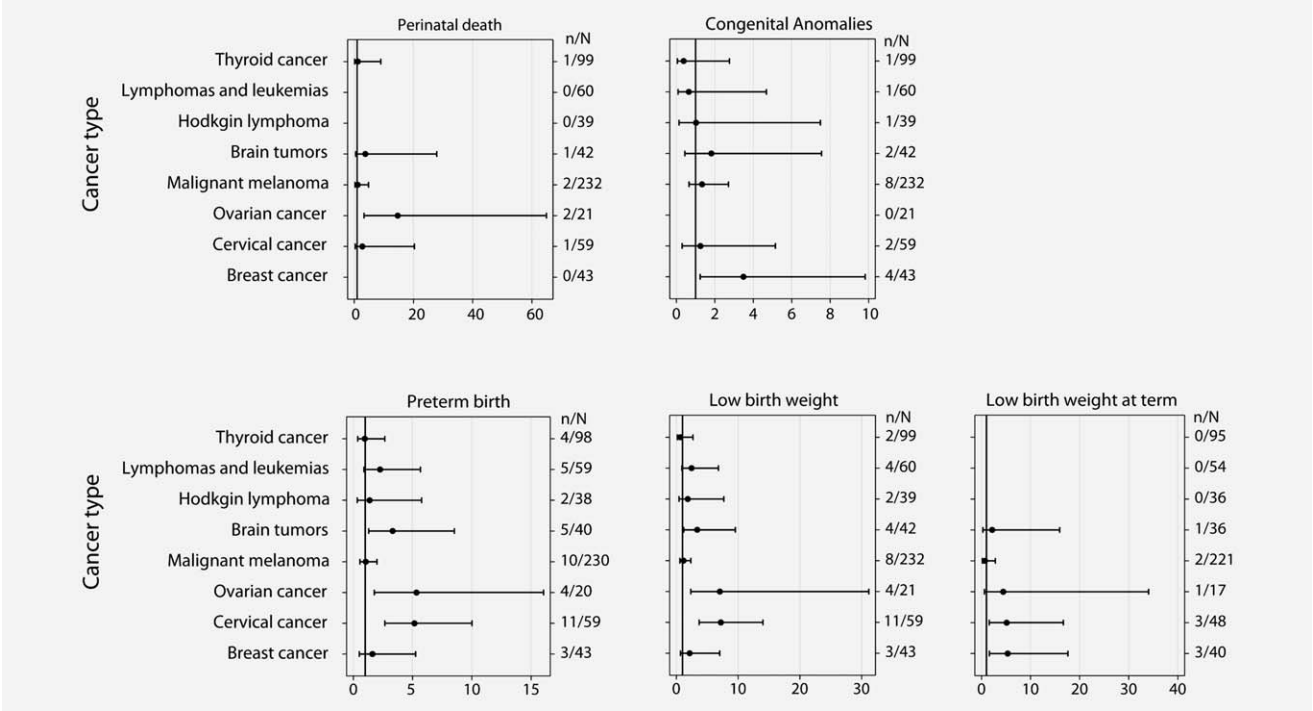

Figure 3. Heading: Effects in the second pregnancy for primiparous females. Footnote: Effects in the second pregnancy for selected cancer types in comparison with the controls, displayed as OR with 95% CI (logarithmic scale). Number of events (*n*) and total number of births (*N*) in each subgroup at right *y*-axis. Reference line = 1.

Pre-eclampsia was more frequent among primiparous female survivors than controls, but not among nulliparous. This might be due to increased risk associated with potentially higher biologic age because of cancer treatment and longer interbirth intervals.[29] Mean interbirth intervals for survivors were 5.9 years and for controls 3.7 years, $P < 0.001$).

To select a cohort almost similar to the Norwegian hospital-based study, we excluded malignant melanoma survivors.[10] Malignant melanoma is the most frequent cancer type in our population-based cohort of survivors, and the vast majority had low stage disease, only requiring local surgery. Such patients are usually not referred to cancer centers. We were not able to reproduce the elevated risks of congenital anomalies among survivors of this subcohort, but the reduced birth weight in postcancer offspring of female survivors was more evident and similar to that reported in the former study.[10]

Our findings for female cancer survivors suggest that the relation between cancer treatment and pregnancy outcomes may be modified by parity, at least for some outcomes. In the general population, the absolute risks of adverse birth outcomes like pre-eclampsia, growth retardation and preterm birth decrease from first to second pregnancy. This risk reduction is not clearly seen for the cancer survivors, since the primiparous seem to have a higher relative risk pattern than the nulliparous. Could cancer treatment accelerate the biological age in such a way that the usual risk reduction associated with primiparity is concealed by an opposite risk increase due to higher biological age? If so, adjustment for chronological age would represent residual confounding. Further, there might be a "healthy mother effect" where primiparous women more easily may choose to start a pregnancy due to previous experience compared to nulliparous women, who may want to condition on feeling healthy before starting a pregnancy.

This large controlled population-based study covers all adult cancer survivors for the period 1967 to 2004, with their registered offspring. We have presented birth outcomes for all cancer types combined, in subgroups based on parity and for several of the most frequent cancer types among adolescents and young adults. The registries have nearly complete information on all key variables and there is negligible loss to follow-up. A methodological strength is the sibship design, which enables us to compare birth outcomes after cancer with those before cancer within the same women, providing an indirect control of confounding. As the birth outcomes before cancer did not differ significantly from those of the controls, it is unlikely that unmeasured confounding factors explain the postcancer results.

In conclusion, postcancer pregnancies were associated with a significantly higher risk of preterm birth for female survivors, more so in offspring of primiparous than nulliparous women. Primiparous female survivors also had LBW babies, pre-eclampsia and cesarean sections more frequently than controls, as opposed to nulliparous survivors. The outcomes in offspring of male survivors did not differ from

those of the general population, but male survivors more frequently used IVF/ICSI to conceive than their controls. We did not find a significantly increased risk of congenital anomalies or perinatal death among infants parented by cancer survivors, at least not when births occurred more than 2 years after diagnosis. For counseling of the growing population of survivors of adolescent and adult cancer, these results are reassuring, but close follow-up should be offered pregnant female survivors. Our results call attention to parity, which might matter for female cancer survivors.

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References

1. Schover LR. Motivation for parenthood after cancer: a review. *J Natl Cancer Inst Monogr* 2005;34: 2–5.
2. Stensheim H, Cvancarova M, Møller B, et al. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. *Int J Cancer* 2011;129:1225–36.
3. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obstet Gynecol* 2002;187:1070–80.
4. Chow EJ, Kamineni A, Daling JR, et al. Reproductive outcomes in male childhood cancer survivors: a linked cancer-birth registry analysis. *Arch Pediatr Adolesc Med* 2009;163:887–94.
5. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of partners of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2003;21:716–21.
6. Signorello LB, Cohen SS, Bosetti C. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst* 2006;98:1453–61.
7. Winther JF, Boice JD, Jr, Frederiksen K, et al. Radiotherapy for childhood cancer and risk for congenital malformations in offspring: a population-based cohort study. *Clin Genet* 2009; 75:50–6.
8. Winther JF, Boice JD, Jr, Mulvihill JJ, et al. Chromosomal abnormalities among offspring of childhood-cancer survivors in Denmark: a population-based study. *Am J Hum Genet* 2004; 74:1282–85.
9. Madanat-Harjuoja LM, Malila N, Lähteenmäki PM, et al. Preterm delivery among female survivors of childhood, adolescent and young adulthood cancer. *Int J Cancer* 2010;127:1669–79.
10. Magelssen H, Melve KK, Skjærven R, et al. Parenthood probability and pregnancy outcome in patients with a cancer diagnosis during adolescence and young adulthood. *Hum Reprod* 2008; 23:178–86.
11. Dalberg K, Eriksson J, Holmberg L. Birth outcome in women with previously treated breast cancer—a population-based cohort study from Sweden. *PLoS Med* 2006;3:e336.
12. Jakobsson M, Gissler M, Sainio S, et al. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2007;109:309–13.
13. Langagergaard V, Gislum M, Skriver MV, et al. Birth outcome in women with breast cancer. *Br J Cancer* 2006;94:142–6.
14. Langagergaard V, Puho EH, Lash TL, et al. Birth outcome in Danish women with cutaneous malignant melanoma. *Melanoma Res* 2007;17:31–6.
15. Langagergaard V, Horvath-Puho E, Nørgård M, et al. Hodgkin's disease and birth outcome: a Danish nationwide cohort study. *Br J Cancer* 2008;98:183–8.
16. Ståhl O, Boyd HA, Giwercman A, et al. Risk of birth abnormalities in the offspring of men with a history of cancer: a cohort study using danish and Swedish national registries. *J Natl Cancer Inst* 2011;103:398–406.
17. Wilcox AJ. Fertility and pregnancy. An epidemiologic perspective. New York: Oxford University Press, 2010. 324 p.
18. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;45: 1218–31.
19. Cancer in Norway 2005. Available at: http://www.kreftregisteret.no/no/Generelt/Publikasjoner/Cancer-in-Norway/Cancer-in-Norway-2005/. Accessed December 12, 2012.
20. Stensheim H, Møller B, van Dijk T, et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009; 27:45–51.
21. The Medical Birth Registry of Norway. Avaialble at: http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3320:1:0:0:::0:0. Accessed December 12, 2012.
22. Irgens LM. The Medical Birth Registry of Norway. *Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand* 2000;79:435–9.
23. Statistics Norway. Available at: http://www.ssb.no/english/. Accessed December 12, 2012.
24. EUROCAT; European surveillance of congenital anomalies. Available at: http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/malformationcodingguides. Accessed December 12, 2012.
25. Skjærven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440–9.
26. Sankila R, Heinävaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect". *Am J Obstet Gynecol* 1994;170:818–23.
27. Dow KH. Having children after breast cancer. *Cancer Pract* 1994;2:407–13.
28. Malamos NA, Stathopoulos GP, Keramopoulos A, et al. Pregnancy and offspring after the appearance of breast cancer. *Oncology* 1996;53: 471–5.
29. Skjærven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002;346:33–8.