

Effects of early maternal cancer and fertility treatment on the risk of adverse birth outcomes

Cathrine Everhøj,^a Filippa Nyboe Norsker,^a Catherine Rechner,^b Sofie de Fine Licht,^a Thomas T Nielsen,^a Susanne K. Kjær,^{c,d} Allan Jensen,^e Marie Hargreave,^c Jane Christensen,^f Federica Belmonte,^f Stine Kjaer Urhoj,^g Katrine Strandberg-Larsen,^g Jeanette F Winther,^{a,h} and Line Kenborg^{a*}

^aChildhood Cancer Research Group, Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden 49, Copenhagen 2100, Denmark

^bDepartment of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

^cVirus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark

^dDepartment of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

^eLifestyle, Reproduction and Cancer, Danish Cancer Society Research Center, Copenhagen, Denmark

^fStatistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark

^gSection of Epidemiology, Department of Public Health, University of Copenhagen, Denmark

^hDepartment of Clinical Medicine, Faculty of Health, Aarhus University and University Hospital, Aarhus, Denmark

Summary

Background Early maternal cancer and fertility treatment each increase the risk for adverse birth outcomes, but the joint effect of these outcomes has not yet been reported. Thus, the aim was to assess the individual and joint effect of maternal cancer and fertility treatment on the risk for adverse birth outcomes.

Methods This population-based cohort study included 5487 live-born singletons identified in the Danish Medical Birth Register (1994–2016) of mothers with previous cancer (<40 years) recorded in the Danish Cancer Registry (1955–2014). We randomly selected 80,262 live-born singletons of mothers with no cancer <40 years matched to mothers with cancer by birth year and month. We calculated odds ratios (ORs) for preterm birth, low birth weight (LBW) (<2500 g) and small for gestational age (SGA), mean differences in birth weight in grams, and additional cases of preterm birth (gestational age <259 days) per 100,000 person-years. Multiplicative and additive interaction of maternal cancer and fertility treatment was compared with outcomes of children conceived naturally to mothers with no maternal cancer (reference group).

Findings Among 84,332 live-born singletons, increased ORs for preterm birth were observed among children born to mothers with previous cancer (1.48, 95% confidence interval [CI] 1.33–1.65) or after fertility treatment (1.43, 95% 1.28–1.61), with 22 additional cases of preterm birth among both group of children (95% CI 15–29; 95% CI 14–30). In the joint analyses, the OR for SGA for children born after fertility treatment to mothers with previous cancer was similar to that of the reference group (OR 1.02, 95% CI 0.72–1.44, *P* for interaction=0.52). Children with both exposures had increased ORs for LBW (1.86, 95% CI 1.17–2.96, *P* for interaction=0.06) and preterm birth (2.31, 95% CI 1.66–3.20, *P* for interaction = 0.56), with 61 additional cases of preterm birth (95% CI 27–95, *P* for interaction=0.26) over that of children in the reference group. The mean birth weight was also lower in children born to mothers with both exposures (-140 g, 95% CI -215; -65) (*P* for interaction=0.06) but decreased to -22 g (95% CI -76; 31) after adjustment for GA.

Interpretation Although we did not find any statistically significant additive interaction between maternal cancer and fertility treatment, children born after fertility treatment of mothers with previous cancer were at increased risk for adverse birth outcomes. Thus, pregnant women with both exposures need close follow-up during pregnancy.

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*Corresponding author.

E-mail address: kenborg@cancer.dk (L. Kenborg).

Research in context

Evidence before this study

Several studies have previously assessed the exposure of maternal cancer or fertility treatment on the risk for adverse birth outcome, which individually have been associated with an increased risk for adverse birth outcomes in the offspring. We searched PubMed without any date restrictions to see if any studies investigated the joint effect of the two exposures using the keywords “cancer” and “fertility treatment”/“ART” and “birth outcomes”/“low birth weight”/“gestational age”/“preterm birth”. The final searches were done on January 26, 2022. We did not find any studies that investigated the joint effect of maternal cancer and fertility treatment on the risk for adverse birth outcomes.

Added value of this study

To our knowledge, this is the first study assessing both the individual and joint effect of maternal cancer and fertility treatment on the risk for adverse birth outcomes. Using a population-based design with both exposure and outcomes identified in nationwide registries, we report mean differences in birth weight and additional cases of preterm birth, which is directly interpretable in terms of adverse health impact on the children. Although we did not find any additive interaction between maternal cancer and fertility treatment, children born after fertility treatment of mothers with previous cancer were at increased risk for being born preterm and with a low birth weight.

Implications of all the available evidence

Our findings add new knowledge to the results from previous studies assessing the individual exposure of maternal cancer and fertility treatment on the risk of adverse birth outcomes and provide evidence for close follow-up of pregnant women with a history of cancer and fertility treatment. Further studies are needed to clarify the association between cancer treatment and treatment-related complications on the risk for adverse birth outcomes in these women.

Introduction

With advances in cancer treatment, the five-year survival of children, adolescents, and young adults (AYA) with cancer has improved substantially, to approximately 80%.¹ The improved survival comes, however, at a price, as a high proportion of the survivors develop health problems that can influence their quality of life.^{2–4} Serious but non-fatal complications include gonadal dysfunction and infertility,⁵ which lower the probability of parenthood by up to 50% in early-onset cancer survivors.⁶ Thus, some female survivors may need fertility treatment to improve their chances of pregnancy.⁷

An increasing number of children are born after fertility treatment, comprising 10.5% of all Danish children born in 2019.⁸ Thus, concern has been raised about the effect of fertility treatment on perinatal health.⁹ Several studies have shown that children born following fertility treatment have twice the rate of preterm birth and a 50–70% increase in risk for being born small for gestational age (SGA) and with a low birth weight (LBW).¹⁰ The same adverse outcomes have been reported in children conceived by female cancer survivors,^{11–16} however to date, no studies have assessed the combined effect of previous cancer and fertility treatment on perinatal health. Thus, the aim of the present study was to investigate the individual and joint effect of early maternal cancer and fertility treatment on the risk for adverse birth outcomes in a population- and register-based cohort study of 85,749 live-born children.

Based on previous findings, our hypothesis was that joint exposure to cancer and fertility treatment results in a higher risk for adverse birth outcomes than each of the two exposures. We assessed the individual effect of maternal cancer by comparing birth outcomes of children born to mothers with a history of cancer to outcomes of children born to mothers with no cancer. Similarly, outcomes of children born after fertility treatment were compared to outcomes of children conceived naturally. Finally, we assessed the joint effect of both exposures by comparing birth outcomes of children born after fertility treatment of mothers with a history of cancer to outcomes of children conceived naturally to mothers with no cancer.

Methods

Study population

The study population was identified in the Danish Medical Birth Register¹⁷ for the period between January 1, 1994, when the *In Vitro* fertilization (IVF) Register was established, and December 31, 2016. We included all 5914 live-born children of 19,790 females with cancer diagnosed before the age of 40 years in the Danish Cancer Registry in the period 1955–2014 (see flow chart in Fig. S1). The Cancer Registry, founded in 1942, contains records of virtually all malignant neoplasms in Denmark since 1943.¹⁸ We included all 85,948 live-born children of 186,091 women in a comparison group. The mothers were randomly selected from the Danish Civil Registration System by density sampling, matched to mothers with cancer on year and month of birth, and were without a registration of a cancer diagnosis in the Danish Cancer Registry. We included only children born after the index date of mothers ≥ 15 years of age who lived in Denmark at the time of the cancer diagnosis and who had not been sterilised according to the National Hospital Register.

We excluded children born within 6 months of the cancer diagnosis, from multiple pregnancies and with missing gestational age (GA) or with a GA <22 weeks. Finally, we also excluded children with implausible foetal growth registrations for GA based on criteria for birthweight and gestational age combinations established by Alexander et al.,¹⁹ leaving 85,749 children (5487 children of mothers with early-onset cancer and 80,262 comparison children) for study.

Information on assisted reproductive technology (ART) and intrauterine insemination (IUI)

Linkage to the Danish IVF Register identified children born after ART (including IVF, intracytoplasmic sperm injection (ICSI), and frozen/thawed embryo transfer (FET)) and IUI. Since January 1, 1994, all ART procedures at private and public clinics have been reported on a statutory basis to the Register, including information on IUI since 2006. Infertile couples and single women are offered up to three completed IVF or ICSI transfer cycles or oocyte recipient cycles with fresh embryos, an unrestricted number of cycles with FET, and 3–6 IUI in public fertility clinics free of charge when <41 years at referral.²⁰ Fertility treatment is available without reimbursement for women <46 years in private fertility clinics, with virtually no limit on the number of treatments.²¹ A child was considered to be born after fertility treatment (both ART and IUI) if conceived within 14 days of the treatment date recorded in the IVF Register (14 days before to 14 days after conception).²² Date of conception was defined as 14 days after the first day of the latest menstrual period and estimated by subtracting GA from date of birth and adding 14 days.

Definition of exposure to maternal cancer and fertility treatment

The two exposures in the study were maternal cancer and fertility treatment. A child was born to a mother with maternal cancer, if the mother was registered with a cancer diagnosis in the Danish Cancer Registry < age 40 years at least six months before giving birth. We considered a child to be born after fertility treatment, if the mother was registered with a fertility treatment in the Danish IVF Register and the child was conceived within 14 days of the treatment date. Finally, a child was exposed to both maternal cancer and fertility treatment if born after fertility treatment of a mother diagnosed with cancer prior to birth.

Adverse birth outcomes

We obtained information on birth weight and GA from the Medical Birth Register. Preterm birth was defined as <37 weeks of gestation (i.e. <259 days) and LBW as birth weight <2500 g. We also included information on

mean birth weight and SGA, defined as <10th percentile of the sex- and gestational-specific birth weight, based on a Scandinavian intrauterine foetal growth standard.²³

Information on potential confounders

Data on all mothers were linked to the nationwide Population Education Register to obtain the highest completed educational level, as a proxy for socioeconomic status.²⁴ From the Medical Birth Register, we also ascertained maternal parity, year of birth, maternal smoking during pregnancy, and pre-pregnancy body mass index (BMI). Registration of maternal smoking and BMI began in 1997 and 2003, respectively, and the information was available for 80,396 (94%) and 53,338 (63%) of the children.

Statistical analysis

The separate and joint effects of maternal cancer and fertility treatment, including the specific treatment (IUI, IVF, ICSI), were assessed in logistic regression models for odds ratios (ORs) with 95% confidence intervals (CIs) for LBW, preterm birth, and SGA. Linear regression models were used to compare mean differences (MDs) in birth weight in grams. We also used the Aalen additive hazards model with GA in days as the underlying time scale to analyze the separate and joint effects of maternal cancer and fertility treatment on the risk for preterm birth. The model allows estimation of the additional number of preterm births associated with the two exposures expressed as additional cases of preterm birth per 100,000 person-years.²⁵ The significance of the interaction between maternal cancer and fertility treatment was assessed in a Wald test. As some of the mothers gave birth to more than one child during the study period, we used the method of robust calculation of CIs to adjust the standard errors for clusters in the same mother.

We analysed the joint effect of maternal cancer and fertility treatment with that of children born to mothers with none of the exposures as the reference group. As we used multiplicative models for LBW and SGA, the potential interaction between maternal cancer and fertility treatment was assessed by adding a product term of the two variables to the model.²⁶ Additive interaction is often considered most clinically relevant. Thus, we calculated relative excess risk due to interaction (RERI) with 95% CIs to assess deviation from additivity.²⁷ RERI >0 represents a synergistic interaction. The joint analyses were also conducted for children born of mothers who had childhood (<15 years old at diagnosis) or AYA (15–39 years) cancer.

All results were presented from unadjusted analyses as well as from analyses adjusted for confounders identified *a priori*: year of birth (1994–1998, 1999–2003,

2004–2008, 2009–2012, 2013–2016), maternal parity (1, ≥ 2), maternal age at delivery (<30, 30–34, 35–39, ≥ 40 years), and highest completed maternal educational level (short: ≤ 9 , medium: 10–12, long: ≥ 12 years). Models of LBW and MDs in birth weight were also adjusted for GA at birth (<37, 37–39, 40, ≥ 41 weeks). Finally, we conducted sensitivity analyses with adjustment for smoking during pregnancy (yes, no) and pre-pregnancy BMI (missing information, <18.5, 18.5–24.9, 25–29.9, ≥ 30). Due to the higher number of children with missing information on maternal BMI than smoking, we conducted the analyses adjusting for BMI using the missing indicator method. Statistical significance was defined as a two-sided *P* value of ≤ 0.05 . All analyses were conducted in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina) and R, version 3.6.3, with the *timereg* package (R Foundation for Statistical Computing).

Ethical approval

With reference to the EU General Data Protection Regulation, the research project is listed in a local database at the Danish Cancer Society (2019-DCRC-0028), where all active research projects using personal data have to be archived. The registration in the database replaces the original study approval given by the Danish Data Protection Agency (J.nr. 2013-41-2228).

Role of the funding source

The funders had no role in the study design, data collection, analysis, interpretation, the writing of the report, and in the decision to submit the paper for publication. CE, FB, and LK had full access to all the data in the study and verified data. LK is the corresponding author and had final responsibility for the decision to submit for publication.

Results

Descriptive results

The final cohort consisted of 85,749 children, of whom 5487 (6%) were born to mothers with early-onset cancer and 4722 (6%) after fertility treatment (Table 1). A higher percentage of children conceived after fertility treatment was born as the first child and to mothers ≥ 35 years at birth, who had long education and did not smoke during pregnancy compared to children conceived naturally. The median age at maternal cancer was slightly higher for children conceived after fertility treatment (27 years, interquartile range (IQR) 21–31) than for those conceived naturally (25 years, IQR 20–19). Mothers who had received abdominal or pelvic irradiation gave birth to 25 children conceived naturally and <5 children after fertility treatment. Finally, mothers with previous cancer had more often been treated

with IUI (31%) and egg donation (6%), but not ICSI (20%), than mothers without cancer (IUI: 27%; egg donation: 1%; ICSI: 26%).

Separate effects of maternal cancer and fertility treatment

Both maternal cancer and any type of fertility treatment was each individually associated with an increased OR for LBW or a lower mean birth weight before adjustment for GA (Table 2) (unadjusted estimates are seen in Table S1). For children born to mothers with previous cancer, the OR for SGA was lower than that of children born to mothers with no cancer (0.86, 95% CI 0.78–0.96). However, the OR for preterm birth was increased among the children (1.48, 95% CI 1.33–1.65) and 22 additional cases of preterm birth per 100,000 person-years (95% CI 15–29) were observed. Likewise, an OR of 1.43 (95% CI 1.28–1.61) for preterm birth and 22 more cases of preterm birth per 100,000 person-years (95% CI 14–30) were found among children conceived after fertility treatment than among children conceived naturally. When we examined the specific ART procedures (IVF and ICSI) and IUI, we found that children born after either IVF or ICSI treatment had a lower mean birth weight than children conceived naturally in the fully adjusted model. The ORs for preterm birth were also increased (IVF: 1.68, 95% CI 1.41–2.01; ICSI 1.40, 95% CI 1.13–1.74) with 36 (95% CI 21–52) and 21 (95% CI 5–36) additional cases of preterm birth per 100,000 person-years (Table 2).

Joint effect of maternal cancer and fertility treatment

The adjusted estimates of the joint effect of maternal cancer and fertility treatment are summarised in Figure 1, with children conceived naturally to mothers with no history of cancer constituting the reference group. The adjusted and unadjusted estimates for all four birth outcomes are shown in Tables S2 and S3.

In the fully adjusted analyses, we found that the OR for LBW was highest in children born to mothers with both exposures (OR 1.86, 95% CI 1.17–2.96; *P* for multiplicative interaction = 0.06) (Figure 1). Thus, the joint effect of childhood cancer and fertility treatment on the multiplicative scale tended to exceed the sum of individual effects. The mean birth weight of children born to mothers with both exposures was lower without adjustment for GA at birth (MD: -140, 95% CI -215; -65) (*P* for additive interaction = 0.06) but attenuated to -22 (95% CI -76; 31, *P* = 0.50) after further adjustment for GA (Table S3). The highest OR for preterm birth was also found in children born to mothers with both exposures (OR 2.31, 95% CI 1.66–3.20, *P* for multiplicative interaction = 0.56). Furthermore, more additional cases of preterm birth per 100,000 person-years were observed among the double exposed children (61, 95%

	All children	Children conceived naturally		Children conceived after fertility treatment	
		Mothers without cancer	Mothers with previous cancer	Mothers without cancer	Mothers with previous cancer
No. (%) of children	85,749	75,914	5113	4348	374
Children					
Year child's birth (%)					
1994–1998	12,198 (14)	11,256 (15)	716 (14)	214 (5)	12 (3)
1999–2003	17,494 (20)	15,921 (21)	1005 (20)	533 (12)	35 (9)
2004–2008	20,286 (24)	18,235 (24)	1171 (23)	824 (19)	56 (15)
2009–2012	17,533 (20)	15,117 (20)	1067 (21)	1244 (29)	105 (28)
2013–2016	18,238 (21)	15,385 (20)	1154 (23)	1533 (35)	166 (44)
Gestational age (weeks) (%)					
Median gestational age in days (IQR)	280 (273–287)	280 (273–287)	280 (272–287)	280 (271–286)	276 (268–283)
<32	642 (1)	523 (1)	57 (1)	51 (1)	11 (3)
32–36	3789 (4)	3174 (4)	302 (6)	281 (6)	32 (9)
37–39	34,893 (41)	30,847 (41)	2056 (40)	1806 (42)	184 (49)
40	24,426 (28)	21,753 (29)	1389 (27)	1198 (28)	86 (23)
>41	21,999 (26)	19,617 (26)	1309 (26)	1012 (23)	61 (16)
Mothers					
Maternal age at birth (years) (%)					
Median (IQR)	32 (29–35)	32 (29–35)	32 (29–35)	35 (32–38)	35 (31–37)
<30	25,281 (29)	23,151 (31)	1597 (31)	482 (11)	51 (14)
30–34	33,297 (39)	29,603 (39)	2055 (40)	1513 (35)	126 (34)
35–39	22,202 (26)	19,029 (25)	1232 (24)	1776 (41)	165 (44)
≥40	4969 (6)	4131 (5)	229 (5)	577 (13)	32 (9)
Parity (%)					
1	31,558 (37)	26,587 (35)	2,055 (40)	2674 (62)	242 (65)
≥1	53,473 (62)	48,678 (64)	3033 (59)	1633 (38)	<130 ^a
Missing data	718 (1)	649 (1)	25 (1)	41 (1)	≤5 ^a
Education (%)					
Short (7–9 years)	9429 (11)	8628 (11)	524 (10)	265 (6)	<20 ^a
Medium (10–12 years)	31,226 (36)	27,886 (37)	1826 (36)	1401 (32)	113 (30)
Long (>12 years)	44,473 (52)	38,845 (51)	2723 (53)	2657 (61)	248 (66)
Missing data	621 (1)	555 (1)	40 (1)	25 (1)	≤5 ^a
Smoking during pregnancy (%)					
Smoker	12,270 (14)	11,299 (15)	655 (13)	287 (7)	29 (8)
Non-smoker	68,126 (79)	59,760 (79)	4121 (81)	3907 (90)	338 (90)
Missing data	5353 (6)	4855 (6)	337 (7)	154 (4)	7 (2)
Pre-pregnancy BMI (%)					
<18.5	2053 (2)	1793 (2)	140 (3)	115 (3)	≤5 ^a
18.5–24.9	33,769 (39)	29,299 (39)	2089 (41)	2174 (50)	207 (55)
25–29.9	11,384 (13)	9831 (13)	681 (13)	797 (18)	75 (20)
≥ 30	6877 (8)	6039 (8)	375 (7)	426 (10)	≤40 ^a
Missing	31,666 (37)	28,952 (38)	1828 (36)	836 (19)	50 (13)
Year of maternal cancer diagnosis (%)					
1958–1979			235 (5)	–	6 (2)
1980–1989			568 (11)		35 (9)
1990–1999			1899 (37)	–	76 (20)
2000–2014			2411 (47)	–	257 (69)
Age at maternal cancer diagnosis (years) (%)					
Median (IQR)			25 (20–29)	–	27 (21–31)
<5			271 (5)	–	13 (3)
5–9			189 (4)	–	10 (3)

Table 1 (Continued)

	All children	Children conceived naturally		Children conceived after fertility treatment	
		Mothers without cancer	Mothers with previous cancer	Mothers without cancer	Mothers with previous cancer
10–14		271 (5)	–	14 (4)	
15–19		504 (10)	–	30 (8)	
20–24		1162 (23)	–	67 (18)	
25–29		1603 (32)	–	105 (28)	
30–34		885 (17)	–	107 (29)	
35–39		228 (4)	–	28 (7)	
Type of maternal cancer (%)					
Leukaemia		273 (5)	–	17 (5)	
Lymphomas		485 (9)	–	25 (7)	
Central nervous system tumor		704 (14)	–	59 (16)	
Neuroblastoma		45 (1)	–	–	
Retinoblastoma		44 (1)	–	≤5 ^a	
Renal tumours		73 (1)	–	10 (3)	
Hepatic tumours		≤5 ^a	–	≤5 ^a	
Bone tumours		81 (2)	–	≤5 ^a	
Soft tissue sarcomas		193 (4)	–	≤5 ^a	
Carcinomas and other malignant epithelial neoplasms					
Thyroid		360 (7)	–	21 (6)	
Cervix		387 (8)	–	48 (13)	
Uterus		≤15 ^a	–	≤5 ^a	
Breast		269 (5)	–	21 (6)	
Stomach and colon		39 (1)	–	≤5 ^a	
Urinary bladder		24 (0)	–	≤5 ^a	
Melanoma		1625 (32)	–	119 (32)	
Germ-cell					
Ovary		76 (1)	–	7 (2)	
Other germ-cell		37 (1)	–	7 (2)	
Other and unspecified malignant neoplasms		382 (8)	–	21 (6)	
Irradiation during cancer treatment ^b (%)					
No		4428 (87)	–	332 (89)	
Yes		583 (11)	–	36 (9)	
Abdomen/pelvis		25	–	≤5 ^a	
Missing data		102 (2)	–	≤10 ^a	
Maternal fertility treatment (%)					
IVF		–	1464 (34)	119 (32)	
ICSI		–	1149 (26)	74 (20)	
IUI		–	1191 (27)	116 (31)	
FER		–	454 (10)	38 (10)	
ED		–	30 (1)	21 (6)	
TESA or missing data		–	60 (1)	6 (2)	

Table 1: Characteristics of children and their mothers by mode of conception and cancer status.
Abbreviations: ED, egg donation; FER, frozen embryo replacement; ICSI, intracytoplasmic sperm injection; IUI, Intrauterine insemination; IQR, interquartile range; IVF, *In vitro* fertilization; TESA, testicular sperm aspiration.
^a If five or fewer events were observed in a group, ≤5 was reported because of reporting restrictions of Statistics Denmark.
^b Information on radiotherapy (yes, no) from the Danish Cancer Registry. Mothers who were likely to have received abdominal or pelvic radiation were defined based on the topography of the cancer.

N	Low birth weight (<2500 g)			Small for gestational age ^b		Birth weight			Preterm birth			
	Cases	OR ^c (95% CI)	OR ^d (95% CI)	Cases	OR ^c (95% CI)	Mean in g (SD)	MD in g ^c (95% CI)	MD in g ^d (95% CI)	Cases	OR ^c (95% CI)	Additional preterm births per 100,000 person-years ^c (95% CI)	
Cancer status												
No cancer	78,922	2778	1 (Reference)	1 (Reference)	6432	1 (Reference)	3536 (566.8)	0 (Reference)	0 (Reference)	3913	1 (Reference)	0 (Reference)
Maternal cancer	5410	263	1.38 (1.22–1.58)	1.08 (0.92–1.27)	395	0.86 (0.78–0.96)	3503 (596.2)	-26 (-45;-7)	4 (-11;19)	391	1.48 (1.33–1.65)	22 (15–29)
Mode of conception												
Natural conception	79,687	2769	1 (Reference)	1 (Reference)	6356	1 (Reference)	3539 (565.8)	0 (Reference)	0 (Reference)	4645	1 (Reference)	0 (Reference)
Fertility treatment	4645	272	1.41 (1.23–1.61)	1.16 (0.98–1.38)	471	1.04 (0.94–1.15)	3436 (610.0)	-49 (-68;-30)	-9 (-24;7)	364	1.43 (1.28–1.61)	22 (14–30)
IUI	1289	64	1.25 (0.96–1.62)	1.23 (0.88–1.71)	129	1.08 (0.90–1.31)	3463 (573.3)	-26 (-59;8)	-8 (-36;20)	79	1.16 (0.91–1.41)	10 (-6–20)
IVF	1553	106	1.57 (1.28–1.93)	1.15 (0.88–1.49)	174	1.10 (0.93–1.29)	3389 (637.2)	-92 (-125;-59)	-29 (-55;-4)	147	1.68 (1.41–2.01)	36 (21–52)
ICSI	1200	74	1.49 (1.17–1.90)	1.29 (0.95–1.77)	134	1.17 (0.97–1.40)	3403 (595.8)	-81 (-116;-47)	-39 (-67;-11)	93	1.40 (1.13–1.74)	21 (5–36)

Table 2: Adjusted estimates and 95% confidence intervals for adverse birth outcomes associated with either maternal cancer status or fertility treatment.^a

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, *in vitro* fertilization; MD, mean difference; OR, odds ratio; SD, standard deviation.

^a 1,417 children excluded because of missing information on maternal education, small for gestational age, or maternal parity.

^b Small for gestational age defined as birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, according to the standard of Alexander et al.¹⁹

^c Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, and year at child's birth.

^d Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, year at child's birth, and gestational week at birth.

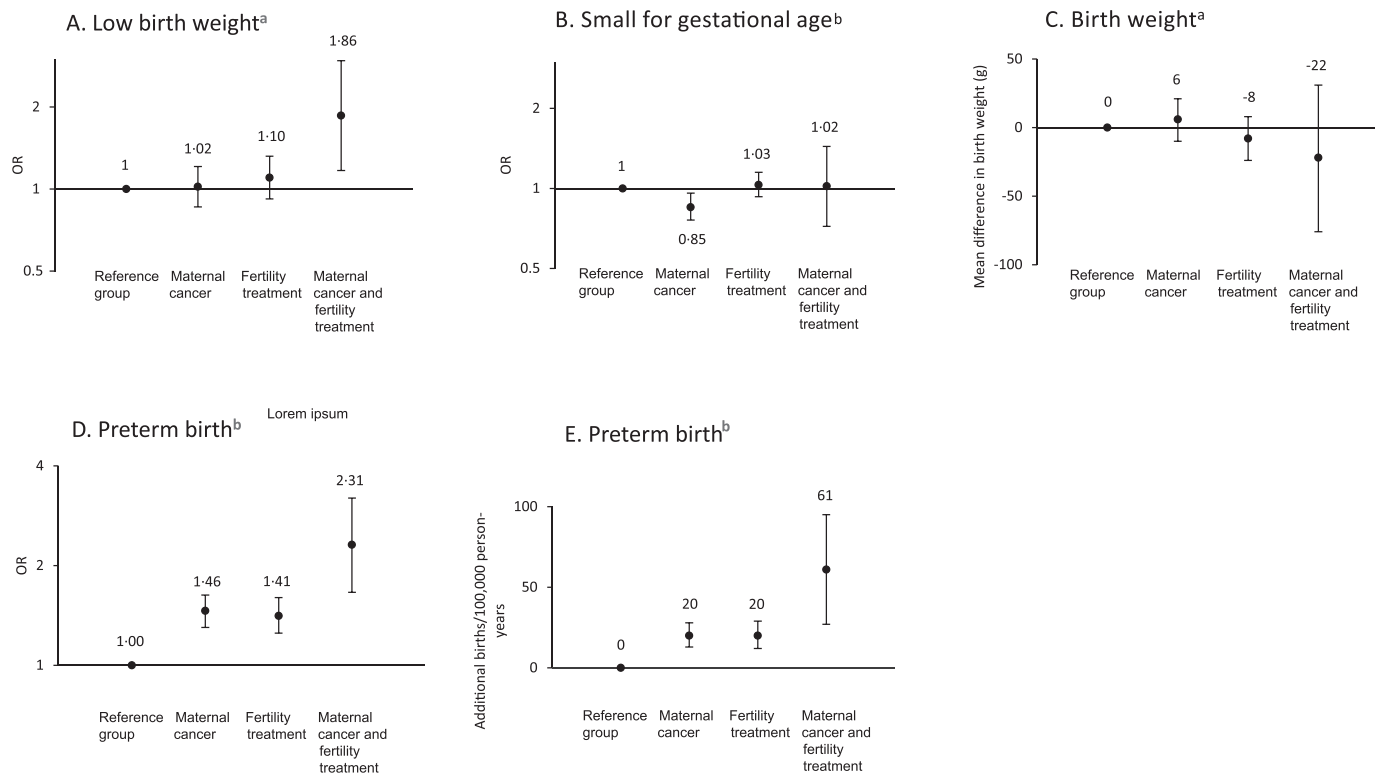


Figure 1. Joint effects with 95% confidence intervals of maternal cancer and mode of conception. A. Odds ratios (OR) for low birth weight associated with the combination of maternal cancer status and mode of conception. B. Small for gestational age associated with the combination of maternal cancer status and mode of conception. C. Mean difference in birth weight associated with the combination of maternal cancer status and mode of conception. D. Odds ratios (OR) for preterm birth associated with the combination of maternal cancer status and mode of conception. E. Additional preterm births per 100,000 person-years associated with the combination of maternal cancer status and mode of conception.

Footnotes to Fig. 1: Reference group = no maternal cancer, no fertility treatment

^aAdjusted for maternal parity, maternal age at birth, maternal highest completed educational level, year at child's birth, and gestational week at birth.

^bAdjusted for maternal parity, maternal age at birth, maternal highest completed educational level, and year at child's birth.

	N	Low birth weight (<2500 g)		Small for gestational age ^b		Birth weight			Preterm birth			
		Cases	OR ^c (95% CI)	OR ^d (95% CI)	Cases	OR ^c (95% CI)	Mean in g (SD)	MD in g ^c (95% CI)	MD in g ^d (95% CI)	Cases	OR ^c (95% CI)	Additional preterm births per 100,000 person-years ^c (95% CI)
Mothers with no history of cancer who conceived naturally	74,646	2543	1 (Reference)	1 (Reference)	5997	1 (Reference)	3541 (564.3)	0 (Reference)	0 (Reference)	3591	1 (Reference)	0 (Reference)
Mothers with no history of cancer who conceived after fertility treatment	4276	235	1.34 (1.16–1.55)	1.10 (0.92–1.32)	435	1.03 (0.93–1.15)	3443 (601.8)	-44 (-64;-24)	-8 (-24;8)	322	1.41 (1.25–1.60)	20 (12–29)
Age at cancer diagnosis <15 years												
Natural conception	727	31	1.44 (1.03–2.00)	0.89 (0.59–1.35)	32	1.12 (0.87–1.43)	3444 (600.0)	-64 (-117;-10)	-15 (-57;26)	66	1.81 (1.40–2.34)	38 (17–59)
Fertility treatment	37	6	5.13 (2.13–12.37)	4.47 (1.33–15.08)	5	1.50 (0.58–3.88)	3241 (875.1)	-226 (-518;65)	-69 (-272;134)	5	2.86 (1.11–7.35)	86 (-33;205)
Age at cancer diagnosis ≥15 years												
Natural conception	4314	188	1.30 (1.11–1.51)	1.05 (0.87–1.27)	287	0.81 (0.71–0.91)	3527 (584.1)	-13 (-34;7)	9 (-7;26)	283	1.39 (1.23–1.58)	17 (10–25)
By fertility treatment	332	31	2.48 (1.70–3.62)	1.64 (1.00–2.71)	31	0.96 (0.66–1.40)	3359 (669.6)	-130 (-206;-54)	-17 (-72;38)	37	2.24 (1.59–3.17)	59 (24–94)
P for interaction ^e			0.17	0.09		0.75		0.16	0.76		0.81	0.49

Table 3: Adjusted estimates and 95% confidence intervals for birth outcomes associated with the combination of age at maternal cancer and mode of conception.^a

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; SD, standard deviation.

^a 1417 children excluded because of missing information on maternal education, small for gestational age, or maternal parity.

^b Small for gestational age defined as birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, according to the standard of Alexander et al.¹⁹

^c Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, and year at child's birth.

^d Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, year at child's birth, and gestational week at birth.

^e Interaction between cancer (none, <15 years, ≥15 years) and fertility treatment (no, yes) on low birth weight, small for gestational age, mean birth weight, and preterm birth.

CI 27–95), but we found no statistically significant additive interaction ($P = 0.26$). Further adjustment for maternal smoking or pre-pregnancy did not change any of the results (not shown). For LBW and SGA, the RERIs were 0.74 (95% CI 0.15–1.63) and 0.12 (95% CI 0.025–0.49), respectively, and thus do not support an additive interaction between maternal cancer and fertility treatment (not shown).

In the analysis by age at cancer diagnosis, we found that children born after fertility treatment of mothers with previous childhood cancer had an OR for LBW of 4.48 (95% CI 1.33–15.08) and preterm birth of 2.86 (95% CI 1.11–7.35) compared with children born of non-exposed mothers. We also observed 86 additional cases of preterm birth (95% CI .33–205) among the children. For children born after fertility treatment of mothers diagnosed with cancer at age 15 to 39 years, the OR of LBW and preterm birth was 1.65 (95% CI 1.00–2.71) and 2.24 (95% CI 1.59–3.17), respectively, while 59 additional cases of preterm births were observed (95% CI 24–94). None of the interactions were significant ($P \geq 0.05$) (Table 3).

Joint effect of maternal cancer and type of fertility treatment

When we examined the joint effect of maternal cancer and type of fertility treatment (IUI, IVF, and ICSI), we found no increase in OR for LBW or SGA (Table 4). A lower mean birth weight was seen for children born after IVF or ICSI to mothers with no history of cancer than in the reference group. The OR for preterm birth was increased for children born after IVF (OR 2.51, 95% CI 1.45–4.33) or ICSI (OR 3.00, 95% CI 1.47–6.10) (P for multiplicative interaction > 0.05). Finally, 72 additional cases of preterm birth per 100,000 person-years (95% CI 9–135, P for additive interaction = 0.68) were observed among children born after IVF of mothers with previous cancer.

Discussion

In this population-based cohort study of 85,749 live-born children, we found that children born of female cancer survivors or after IVF or ICSI were at increased risk for being born preterm. We also combined the two exposures of maternal cancer and fertility treatment and compared them for children of mothers with none of the exposures as the reference group. Children conceived of mothers with both exposures were more often born preterm and with a LBW compared to children in the non-exposed reference group, but with no evidence of an additive interaction between maternal cancer and fertility treatment. We did not find any increased OR for the children being born SGA.

Several studies have reported higher rates of preterm birth before 37 weeks' gestation and LBW in children

born to female cancer survivors, with an overall 1.3- to 3-times higher risk in survivors than in their siblings or the general population.^{12–15,28–31} Similarly, studies have consistently shown up to two-times increased risks for preterm birth and LBW in singletons born after IVF or ICSI in women with no history of cancer.^{32–38} The results of studies of LBW in children born to female cancer survivors or after fertility treatment were, however, inconsistent after adjustment for gestational week at birth. We found that further adjustment for GA attenuated the differences in birth weight and ORs for LBW in all analyses. Gestational age is important in studies of birth outcomes and partly explained the increased risk for a lower birth weight in children born of cancer survivors or after fertility treatment in our study. In contrast to Farland et al.,³⁹ we did not find an increased risk for children being born SGA if conceived after fertility treatment of mothers with previous cancer. Thus, in our study, children born of mothers with both exposures were at increased risk for being born preterm and with a lower birth weight, but appropriate for their gestational age.

Total body irradiation and abdominal or pelvic radiation are associated with impaired volume, muscular elasticity, and blood flow of the uterus,⁴⁰ and have all been suggested as causative factors for the adverse birth outcomes observed in children born to female cancer survivors.^{40,41} In addition, pre-pubertal irradiation has shown to result in severe uterine dysfunction,⁴² which may partly explain our findings of higher risks for adverse birth outcomes among children of female survivors of childhood cancer. Despite the inclusion of 85,749 live-born children, ≤ 5 children were born after fertility treatment of survivors who had received abdominal or pelvic irradiation, which might indicate that survivors after abdominal or pelvic radiation are not offered fertility treatment or not capable of giving birth to a live-born child. The results of a few studies indicate limited evidence for any association between chemotherapy and risk for preterm birth and LBW.⁴³ Thus, the underlying pathophysiology of the increased risk of adverse birth outcomes in non-irradiated female cancer survivors is still unknown. Further studies should be conducted to clarify the roles of surgery and chemotherapy, including specific agents and administered doses, as well as other treatment-related complications and their association with adverse birth outcomes.

Studies have reported a higher frequency of abnormal placentation, placental abruption, uterine bleeding, and placenta previa in pregnancies after IVF, which may induce preterm birth.⁴⁴ In addition, factors related to fertility treatment, including medication and retrieval of a large number of oocytes have been associated with adverse birth outcomes.^{45,46} Higher risks for pregnancy complications, including gestational diabetes mellitus, hypertension, and preeclampsia, have also been reported in women achieving a pregnancy after ART as

	N	Low birth weight (<2500 g)			Small for gestational age ^b		Birth weight			Preterm birth		
		Cases	OR ^c (95% CI)	OR ^d (95% CI)	Cases	OR ^c (95% CI)	Mean in g (SD)	MD in g ^c (95% CI)	MD in g ^d (95% CI)	Cases	OR ^c (95% CI)	Additional preterm births per 100,000 person-years ^c (95% CI)
Mothers with no history of cancer who conceived naturally	74,646	2543	1 (Reference)	1 (Reference)	5997	1 (Reference)	3541 (564.3)	0 (Reference)	0 (Reference)	3591	1 (Reference)	0 (Reference)
Mothers with previous cancer who conceived naturally	5041	226	1.32 (1.15–1.52)	1.02 (0.86–1.21)	359	0.85 (0.76–0.96)	3515 (387.0)	-20 (-40; -1)	6 (-10;21)	349	1.46 (1.30–1.63)	20 (13–28)
Conception by IUI												
No cancer	1176	56	1.22 (0.93–1.61)	1.20 (0.85–1.71)	118	1.08 (0.88–1.31)	3468 (564.6)	-22 (-56; 12)	-7 (-36;22)	69	1.14 (0.89 1.46)	6 (-8–20)
Maternal cancer	113	8	1.88 (0.91–3.87)	1.45 (0.56–3.70)	11	1.03 (0.55–1.93)	3407 (657.5)	-79 (-207; 49)	-10 (-102;81)	10	1.78 (0.93–3.42)	37 (-17–91)
Conception by IVF												
No cancer	1435	94	1.53 (1.23–1.89)	1.11 (0.84–1.46)	164	1.11 (0.94–1.31)	3391 (631.8)	-92 (-126;57)	-32 (-59;5)	132	1.68 (1.39–2.02)	35 (19–50)
Maternal cancer	118	12	2.65 (1.45–4.85)	1.60 (0.71–3.60)	10	0.83 (0.43–1.59)	3371 (702.7)	-118 (-244;8)	8 (-87;103)	15	2.51 (1.45–4.33)	72 (9–135)
Conception by ICSI												
No cancer	1127	66	1.44 (1.11–1.86)	1.23 (0.89–1.71)	125	1.14 (0.94–1.38)	3411 (591.2)	-75 (-110;40)	-37 (-66;9)	85	1.40 (1.11–1.75)	20 (4–35)
Maternal cancer	73	8	3.01 (1.43–6.31)	2.17 (0.81–5.71)	9	1.34 (0.66–2.71)	3286 (655.3)	-200 (-351;50)	-59 (-170;53)	8	3.00 (1.47–6.10)	56 (-18–130)
<i>P</i> for interaction ^e			0.28	0.18		0.67		0.07	0.17		0.92	0.68

Table 4: Adjusted estimates and 95% confidence intervals for birth outcomes associated with the combination of maternal cancer and type of fertility treatment.^a

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, *in vitro* fertilization; MD, mean difference; OR, odds ratio; SD, standard deviation.

^a 1417 children excluded because of missing information on maternal education, small for gestational age, or maternal parity.

^b Small for gestational age defined as birth weight in the bottom 10th percentile for infants of the same sex born on the same gestational week, according to the standard of Alexander et al.¹⁹

^c Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, and year at child's birth.

^d Adjusted for maternal parity, maternal age at birth, maternal highest completed educational level, year at child's birth, and gestational week at birth.

^e Interaction between cancer (no, yes) and type of fertility treatment (IUI, IVF, ICSI) on low birth weight, small for gestational age, mean birth weight, and preterm birth.

well as in pregnant survivors of early-onset cancer.^{47–51} Thus, pregnancy complications might also contribute to the increased risk of preterm births or lower birth weight observed in our study.

The main strengths of our study include unbiased identification of female cancer survivors and birth outcomes from nationwide, population-based registries with virtually complete coverage, clear temporality of exposures and outcomes, as well as limited loss to follow-up. The Danish registries also provided information on important confounders that were included in the analyses. We ascertained information on fertility treatment from a population-based register with mandatory registration of treatments in both public and private clinics in Denmark. As treatment is free of charge, the study was less susceptible to selection related to treatment access. Our study also has several limitations, including lack of detailed information on radiotherapy and chemotherapy drugs and doses. Other limitations include the lack of information on IUI treatments in the IVF Register before 2006 and missing information on fertility drugs. Thus, our results cannot be generalised to women who have only been treated with fertility drugs. In addition, we did not consider pregnancy complications, which increase the risk for preterm birth or having a child SGA. We used a reference to exclude children with implausible birth weights based on their sex and gestational age at birth. However, an increasing proportion of children have been found to be born large for gestational age during the study period,⁵² which might have influenced the relationship between birth weight and gestational age in our study. Finally, as our study population included only live-born children we were unable to assess miscarriage or stillbirths in women who received fertility treatment.

In conclusion, children born to female cancer survivors or after maternal treatment with IVF or ICSI were at increased risk for being born preterm. We also found that children born after fertility treatment of mothers with previous cancer had a higher OR for LBW and were more often born preterm than children of mothers with neither of the exposures, however, with no statistically significant additive interaction between maternal cancer and fertility treatment. The OR was not increased for the children being born SGA, which indicates that the lower birth weight of the children is a consequence of preterm birth and not growth restrictions during pregnancy. For some survivors of early-onset cancer, fertility treatment is the only possibility for having children. Thus, female cancer survivors who become pregnant after fertility treatment should be closely followed up during their pregnancy.

Author contributors

CE, LK, KSL, SUK, and JFW designed the study, while LK, KSL, and SUK supervised the study. LK applied for

data. TTN prepared the data and MH developed the program for identifying children born after fertility treatment. CE, TTN, FB, and LK had access to all data in the study and they accept full responsibility for all data associated with this study. CE, FB, and LK did the statistical analyses, while JC supervised analyses conducted by CE and LK. CE and LK wrote the first draft of the manuscript. All authors interpreted the results and provided critical input in revision. All authors contributed to reviewing and editing multiple versions of the manuscript and they have approved the final manuscript before submission.

Declaration of interests

After finalizing her master thesis and this study, Cathrine Everhøj started as a full time employee at Danske Regioner, which is a public employer organization of the five regions in Denmark responsible for the health-care system. Filippa Nyboe Norsker and Sofie de Fine Licht have finalized their postdoctoral work and started as full time employees at the Danish Medicines Council and AstraZeneca, respectively. None of the other authors has any conflicts of interest.

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Data sharing statement

All data are stored on a secure platform at Statistics Denmark and can only be accessed remotely. The study group welcomes collaboration with other researchers. Study protocols can be planned in collaboration with us, and the data can be analysed accordingly at the server of Statistics Denmark. Access to data can only be made available for researchers who fulfill Danish legal requirements for access to personal sensitive data. Please contact Professor Jeanette Falck Winther (jeanette@cancer.dk) or senior researcher Line Kenborg (kenborg@cancer.dk) for further information.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinnm.2022.101369](https://doi.org/10.1016/j.eclinnm.2022.101369).

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