THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.14909 J. Obstet. Gynaecol. Res. 2021

Pregnancy outcomes in children, adolescents, and young adults that survived cancer: A nationwide survey in Japan

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Abstract

Aim: Recent advances in cancer treatment have improved the prognosis of child, adolescent, and young adult (CAYA) cancer survivors. This study aimed to examine the current status of pregnancy outcomes among female cancer survivors in Japan.

Methods: The first questionnaire was sent to 633 major tertiary institutions certified by the Japan Society of Obstetrics and Gynecology to identify institutions managing cases of pregnant cancer survivors between January 2011 and December 2015. The second questionnaire was sent only to institutions with pregnant cancer survivors during the study period.

Results: We analyzed 2242 singleton deliveries of cancer survivors based on the responses received in the second questionnaire (199/255 responses; 78.0%). The three most frequent types of malignant tumors were uterine cervical (23.4%), breast (17.6%), and thyroid cancers (17.5%). Conception was aided by the use of assisted reproductive technology in 17.0% of the patients. The proportions of mothers aged 35–39.9 and ≥ 40 years were 36.5% and 11.8%, respectively. The prevalence of preterm birth (PTB) at <37, <34, and < 32 weeks' gestation were 16.7%, 6.8%, and 4.3%, respectively. The proportion of infants with low birth weight (LBW) was 18.9%.

Conclusion: The present study findings suggest that advanced maternal age was common among pregnant cancer survivors and these survivors often gave birth to PTB and LBW infants in Japan. The likelihood of adverse pregnancy outcomes should be considered by healthcare providers when planning counseling and perinatal care for cancer survivors.

Key words: assisted reproductive technology, CAYA generation, female cancer survivor, oncofertility, pregnancy outcome.

Received: January 27 2021.
Accepted: June 10 2021.
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Introduction

In recent years, due to advances in cancer treatment, the survival rate of cancer patients has improved, particularly, the prognosis for cancer in the childhood, adolescent, and young adult (CAYA) generation.[1] With this improvement, the health care of the subsequent CAYA generation of cancer survivors has become an issue that needs attention and care. Cancer survivors of CAYA generation often suffer from infertility, as cancer treatments sometimes cause a defect in their reproductive function. Cancer survivors among women considering pregnancy face further concerns about the impact of cancer treatment on their ability to maintain a normal pregnancy and the potential adverse effects on their offspring.[2]

Several studies have assessed complications associated with pregnancy and delivery in female cancer survivors compared to their siblings or the general population. The risk of preterm birth (PTB), in particular, has been reported to increase when cancer survivors are diagnosed during their reproductive life in several large populations, notably in the US Childhood Cancer Survivors Study and the British Childhood Cancer Survivors Study.[3–8] A recent meta-analysis examined the risks of perinatal complications in female cancer survivors diagnosed before the age of 40 years and reported a two-fold increase in the risk of PTB after radiotherapy with respect to perinatal complications that occur after cancer treatment.[9]

Cancer treatment may affect the prospects for pregnancy in the future, and cancer survivors have been reported to be less likely than the general population to become pregnant.[10,11] Nevertheless, many female survivors have the potential to become pregnant.[12–14]

While these findings have been reported in Western countries, studies on pregnancy outcomes of cancer survivors in Japan are limited.[15] No large-scale study of pregnancy outcomes among cancer survivors of the CAYA generation, particularly adolescents and young adults, has been conducted in Japan to date. Therefore, this study aimed to examine the perinatal outcomes of cancer survivors in Japan.

Methods

Study design

This study was a part of the Japan Agency for Medical Research and Development project "development of the infrastructure of oncofertility in Japan" (Principal Investigator: Yutaka Osuga). The objectives of this project were to investigate the current status of fertility-conserving interventions in cancer treatment, to disseminate the most advanced treatment, to develop a new treatment, and to establish a highly ethical medical system necessary for fertility-conserving cancer treatment. This research is the result of the "survey of childbirth of cancer survivors" that is part of this project.

This study was conducted by collecting data using two questionnaires. The first questionnaire was sent to 633 major teaching institutions certified by the Japan Society of Obstetrics and Gynecology (JSOG) in Japan to investigate the presence of pregnant cases of cancer survivors between January 2011 and December 2015. Next, the second questionnaire was sent to institutions managing pregnant cancer survivors. The study protocol was approved by Ehime University Hospital institutional research board (approval No. 1909020) and The University of Tokyo institutional research board (approval No. 11376).

Data collection in the second survey

Information on the pregnant cancer survivors was collected in the second survey. Conception method and maternal age when the gestational sac was confirmed were collected. Conception methods were classified as follows: spontaneous pregnancy, non-assisted reproductive technology (ART), including ovulatory induction and artificial insemination by the husband, and ART, including in vitro fertilization and embryo transfer (IVF-ET), and intracytoplasmic sperm injection (ICSI). Information on the use of frozen eggs, embryos, or ovarian tissue obtained before therapy or during therapy was also collected. In addition, data on multiple pregnancies, miscarriages, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), placenta previa or low-lying placenta, fetal anomalies, delivery week, and infant birth weight were collected. Miscarriage was defined as the loss of fetus at less than 22 weeks of gestation. PIH was defined according to the Japanese Society for the Study of Hypertension in Pregnancy guidelines, which was a previous diagnostic criterion adopted in Japan.[16] PIH was diagnosed when hypertension (systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) occurred after 20 weeks of gestation in subjects without hypertension at less than 20 weeks of gestation. Furthermore, PIH was also diagnosed when proteinuria appeared in subjects with hypertension at less than 20 weeks of gestation.

GDM was diagnosed based on the criteria recommended by JSOG.[17] GDM was diagnosed when at least one of the following criteria during a 75-g oral glucose tolerance test, regardless of gestational age, was present: fasting plasma glucose (PG) of 92–125 mg/dL, 1-h PG ≥180 mg/dL, and 2-h PG ≥153 mg/dL.[17] Placenta previa was diagnosed when the placenta covered the internal os of the uterus or the margin of the placenta reached the histological internal os of the uterus. A low-lying placenta was also diagnosed when the placental margin was within 2 cm of the histological internal os of the uterus. Neither parity nor infant sex was included in this study.

History of malignant tumor in pregnant cancer survivor

Information on the history of malignant tumors was collected. Specifically, the data on type, therapy, and age at diagnosis of malignant tumors were collected. We categorized the patients according to the frequency of the history of malignant tumors. Surgery, chemotherapy, hormone therapy, hematopoietic stem cell transplantation, and other therapies were collected as therapies for malignant tumors.

Pregnancy outcomes in this study

Pregnancy outcomes in this study were miscarriage, PTB at less than 37 weeks of gestation, PTB at less than 34 weeks of gestation, PTB at less than 32 weeks of gestation, PIH, GDM, placenta previa or low-lying placenta, fetal anomalies, and infant birth weight. Low birth weight (LBW) infants were defined as infants with birth weights of <2500 g. Light-for-date infants could not be defined because neither parity nor infant sex was collected in this study.

Statistical analysis

To investigate the difference in pregnancy outcomes among the types of history of malignant tumors, we used a generalized linear mixed-effects model with a logit link function or a general linear mixed-effects model, as appropriate.[18] Details of the statistical analysis are described in the Supporting Information (Appendix S1).

Results

Inclusion of subjects in this study

Of the 633 institutions to which the first questionnaire was sent, 423 institutions responded (response rate, 66.8%); of these, 255 institutions were providing care for pregnant cancer survivors at that time. The second questionnaire was sent to these 255 institutions, which are major teaching institutions certified by JSOG to manage pregnant cancer survivors. We received responses from 199 institutions (response rate was 78.0%).

Details of the inclusion of study subjects are described in Figure S1.

Maternal and neonatal characteristics of study subjects

The three most frequent types of malignant tumors were uterine cervical (23.4%), breast (17.6%), and thyroid cancer (17.5%). The proportion of subjects who were diagnosed during the adolescent and young adult periods was 89.5%. Conception by ART was observed in 17.0% of patients. The proportions of women with gestational sac confirmed at maternal age of 35–39.9 and ≥40 years were 36.5% and 11.8%, respectively. The prevalence of PTB at less than 37, 34, and 32 weeks of gestation were in 16.7%, 6.8%, and 4.3%, respectively. The proportions of women with PIH, GDM, placenta previa or low-lying placenta, and fetal anomalies were 5.1%, 5.9%, 2.5%, and 1.6%, respectively. The percentage of subjects who gave birth to LBW infants in singleton pregnancies was 18.9% (Table 1).

Maternal and neonatal characteristics according to types of a history of malignant tumor

As shown in Table 2, the proportion of women who conceived by ART and PTB at less than 37, 34, and 32 weeks of gestations, and of women with LBW infants were higher in the group with a history of uterine cervical cancer than in those with a history of other types of cancer. The proportion of women receiving chemotherapy, radiation, and hormone therapy was higher in the group with a history of breast cancer than in those with a history of uterine cervical and thyroid cancers. The women with a history of thyroid cancer were younger at the time of malignant tumor diagnosis than those with a history of uterine cervical and breast cancers (Table 2).

Differences in the pregnancy outcomes among types of malignant tumor

In order to analyze the characteristics of perinatal outcomes by primary site of malignancy, pregnant women without a history of cancer were used as the control group for statistical analysis; however, in the population of data collected in the present study,

TABLE 1 Maternal and neonatal characteristics of study subjects

Characteristics	Values
The number of subjects	1946
Type of malignant tumor, *n* (%)	
Uterine cervical cancer	455 (23.4)
Breast cancer	342 (17.6)
Thyroid cancer	341 (17.5)
Malignant tumor other than uterine cervical, breast, and thyroid cancer	808 (41.5)
Blood cancer	177 (9.1)
Ovarian cancer	169 (8.7)
Borderline tumors of the ovary	103 (5.3)
Colorectal cancer	62 (3.2)
Endometrial cancer	55 (2.8)
Gastric cancer	50 (2.6)
Bone and soft tissue tumors	30 (1.5)
Kidney cancer	23 (1.2)
Other cancers	141 (7.3)
Therapy for malignant tumor before conception, *n* (%)	
Operation	
No	258 (13.3)
Yes	1624 (83.5)
Missing data	64 (3.3)
Chemotherapy	
No	1436 (73.8)
Yes	445 (22.9)
Missing data	65 (3.3)
Hormone therapy	
No	1697 (87.2)
Yes	185 (9.5)
Missing data	64 (3.3)
Radiation	
No	1610 (82.7)
Yes	272 (14.0)
Missing data	64 (3.3)
Hematopoietic stem cell transplantation	
No	1863 (95.7)
Yes	19 (1.0)
Missing data	64 (3.3)
Other therapies	
No	1765 (90.7)
Yes	117 (6.0)
Missing data	64 (3.3)
Age when malignant tumor was diagnosed, years, *n* (%)	
<15 years	94 (4.8)
Adolescent and young Adult	1742 (89.5)
15–19.9 years	96 (4.9)
20–24.9 years	210 (10.8)
25–29.9 years	499 (25.6)
30–34.9 years	626 (32.2)
35–39.9 years	311 (16.0)
≥40 years	52 (2.7)
Missing data	58 (3.0)
Conception method, *n* (%)	
Spontaneous	1197 (61.5)
Non-ART (Ovulation induction or AIH)	379 (19.5)
ART	331 (17.0)
Missing data	39 (2.0)
Use of frozen egg, embryo, or ovarian tissue which were obtained before therapy or during therapy, *n* (%)	
No	1898 (97.5)
Natural pregnancy	1326 (69.9)
Timing	115 (6.1)
AIH	92 (4.9)
IVF-ET	272 (14.3)
Missing data	93 (4.9)
Yes	31 (1.6)
ICSI	5 (16.1)
IVF-ET	26 (83.9)
Missing data	17 (0.9)
Maternal age when gestational sac was confirmed, *n* (%)	
<25 years	70 (3.6)
25–29.9 years	281 (14.4)
30–34.9 years	588 (30.2)
35–39.9 years	711 (36.5)
≥40 years	230 (11.8)
Missing data	66 (3.4)
Multiple pregnancies, *n* (%)	26 (1.3)
Obstetric complications, *n* (%)	
Miscarriage	30 (1.5)
Preterm birth at less than 37 weeks of gestation	318 (16.7)
Preterm birth at less than 34 weeks of gestation	130 (6.8)
Preterm birth at less than 32 weeks of gestation	82 (4.3)
Pregnancy induced hypertension	97 (5.1)
Gestational diabetes mellitus	113 (5.9)
Placenta previa or low-lying placenta	47 (2.5)
Fetal anomalies in singleton pregnancies	30 (1.6)
Infant birth weight in singleton pregnancies, gram[a]	2847 (569)
Low birth weight infant in singleton pregnancies, *n* (%)[a]	350 (18.9)

Note: Continuous variables and categorical variables are expressed as mean (SD) and *n* (%), respectively.; [a]*N* = 1854. and Abbreviations: AIH, artificial insemination with husband's semen; ART, assisted reproductive technology; IVF-ET, in vitro fertilization and embryo transfer.

thyroid cancer survivors were used as a reference group because of no available data on pregnant women without previous cancer. There were no epidemiological studies that showed increased risk of pregnancy complications or perinatal outcomes

TABLE 2 Maternal and neonatal characteristics according to types of malignant tumor

Characteristics	Type of malignant tumor			
	History of uterine cervical cancer	History of breast cancer	History of thyroid cancer	History of malignant tumor other than uterine cervical, breast, and thyroid cancer
The number and percentages of subjects	455 (23.4)	342 (17.6)	341 (17.5)	808 (41.5)
Therapy for malignant tumor before conception, *n* (%)				
Operation				
No	17 (3.7)	24 (7.0)	5 (1.5)	212 (26.2)
Yes	428 (94.1)	306 (89.5)	327 (95.9)	563 (69.7)
Missing	10 (2.2)	12 (3.5)	9 (2.6)	33 (4.1)
Chemotherapy				
No	439 (96.5)	225 (65.8)	332 (97.4)	440 (54.5)
Yes	6 (1.3)	105 (30.7)	0 (0.0)	334 (41.3)
Missing	10 (2.2)	12 (3.5)	9 (2.6)	34 (4.2)
Hormone therapy				
No	444 (97.6)	210 (61.4)	324 (95.0)	719 (89.0)
Yes	1 (0.2)	120 (35.1)	8 (2.4)	56 (6.9)
Missing	10 (2.2)	12 (3.5)	9 (2.6)	33 (4.1)
Radiation				
No	445 (97.8)	169 (49.4)	310 (90.9)	686 (84.9)
Yes	0 (0.0)	161 (47.1)	22 (6.5)	89 (11.0)
Missing	10 (2.2)	12 (3.5)	9 (2.6)	33 (4.1)
Hematopoietic stem cell transplantation				
No	–	–	–	756 (93.6)
Yes	–	–	–	19 (2.4)
Missing	–	–	–	33 (4.1)
Other therapies				
No	423 (93.0)	307 (89.8)	311 (91.2)	724 (89.6)
Yes	22 (4.8)	23 (6.7)	21 (6.2)	51 (6.3)
Missing data	10 (2.2)	12 (3.5)	9 (2.6)	33 (4.1)
Age when malignant tumor was diagnosed, years, *n* (%)				
<15 years	5 (1.1)	0 (0.0)	7 (2.1)	82 (10.2)
Adolescent and young adult	432 (94.6)	310 (90.6)	311 (91.2)	689 (85.3)
15–19.9 years	2 (0.4)	0 (0.0)	19 (5.6)	75 (9.3)
20–24.9 years	32 (7.0)	7 (2.1)	50 (14.7)	121 (15.0)
25–29.9 years	119 (26.2)	65 (19.0)	103 (30.2)	212 (26.6)
30–34.9 years	201 (44.2)	141 (41.2)	90 (26.4)	194 (24.0)
35–39.9 years	78 (17.1)	97 (28.4)	49 (14.4)	87 (10.8)
≥40 years	11 (2.4)	26 (7.6)	7 (2.1)	8 (1.0)
Missing data	7 (1.5)	6 (1.8)	16 (4.7)	29 (3.6)
Sex dysfunction, *n* (%)				
No	425 (93.4)	305 (89.2)	321 (94.1)	751 (93.0)
Yes	4 (0.9)	5 (1.5)	3 (0.9)	9 (1.1)
Missing data	25 (5.7)	32 (9.4)	17 (5.0)	48 (5.9)
Conception method, *n* (%)				
Spontaneous	302 (66.4)	234 (68.4)	265 (77.7)	593 (73.4)
Non-ART (Ovulation induction or AIH)	43 (9.5)	18 (5.3)	17 (5.0)	63 (7.8)
ART	92 (20.2)	57 (17.7)	45 (13.2)	96 (11.9)
Missing data	18 (4.0)	33 (9.7)	14 (4.1)	56 (6.9)
Use of frozen egg, embryo, or ovarian tissue which were obtained before therapy or during therapy, *n* (%)				
No	452 (99.3)	323 (94.4)	335 (98.2)	788 (97.5)
Natural pregnancy	293 (64.8)	220 (68.1)	259 (77.3)	554 (70.3)
Timing	18 (4.0)	21 (6.5)	16 (4.8)	60 (7.6)
AIH	34 (7.5)	12 (3.7)	7 (2.1)	39 (5.0)

(*Continues*)

TABLE 2 Continued

Characteristics	Type of malignant tumor			
	History of uterine cervical cancer	History of breast cancer	History of thyroid cancer	History of malignant tumor other than uterine cervical, breast, and thyroid cancer
IVF-ET	91 (20.1)	52 (16.1)	40 (11.9)	89 (11.3)
Missing data	16 (3.5)	18 (5.6)	13 (3.9)	46 (5.8)
Yes	2 (0.4)	15 (4.4)	3 (0.9)	11 (1.4)
ICSI	0 (0.0)	1 (6.7)	0 (0.0)	4 (36.4)
IVF-ET	2 (100)	14 (93.3)	3 (100)	7 (63.6)
Missing data	1 (0.2)	4 (1.2)	3 (0.9)	9 (1.1)
Maternal age when gestational sac was confirmed, *n* (%)				
<25 years	10 (2.2)	1 (0.3)	14 (4.1)	45 (5.6)
25–29.9 years	55 (12.1)	12 (3.5)	51 (15.0)	163 (20.2)
30–34.9 years	160 (35.2)	54 (15.8)	101 (29.6)	273 (33.8)
35–39.9 years	169 (37.1)	178 (52.1)	122 (35.8)	242 (30.0)
≥40 years	44 (9.7)	84 (24.6)	42 (12.3)	60 (7.4)
Missing data	17 (3.7)	13 (3.8)	11 (3.2)	25 (3.1)
Multiple pregnancies, *n* (%)	7 (1.5)	4 (1.2)	6 (1.8)	9 (1.1)
Obstetric complications, *n* (%)				
Miscarriage	8 (1.8)	7 (1.2)	5 (1.5)	10 (1.2)
Preterm birth at less than 37 weeks of gestation	137 (30.5)	44 (13.2)	25 (7.5)	112 (14.6)
Preterm birth at less than 34 weeks of gestation	67 (14.9)	11 (3.3)	8 (2.4)	44 (5.6)
Preterm birth at less than 32 weeks of gestation	42 (9.4)	7 (2.1)	8 (2.4)	25 (3.2)
Pregnancy induced hypertension	15 (3.3)	17 (5.1)	23 (6.9)	42 (5.3)
Gestational diabetes mellitus	31 (6.9)	17 (5.1)	19 (5.7)	46 (5.8)
Placenta previa or low-lying placenta	8 (1.8)	13 (3.9)	5 (1.5)	21 (2.7)
Fetal anomalies in singleton pregnancies	9 (2.0)	4 (1.2)	10 (3.1)	7 (0.9)
Infant birth weight in singleton pregnancies, gram, mean (SD)	2656 (654)	2935 (493)	2924 (493)	2881 (561)
Low birth weight infant in singleton pregnancies, *n* (%)	130 (30.4)	43 (13.5)	38 (12.1)	135 (17.7)

Note: Continuous variables and categorical variables are expressed as mean (SD) and *n* (%), respectively. and Abbreviations: AIH, artificial insemination with husband's semen; ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; IVF-ET, in vitro fertilization and embryo transfer.

among thyroid cancer survivors to date; therefore, we chose thyroid cancer survivors as a reference group in this study (Table 3).

The subjects with a history of uterine cervical cancer had significantly higher odds of having PTB at less than 37, 34, and 32 weeks of gestations and LBW infants, than those with a history of thyroid cancer. Infant birth weight was significantly lower in subjects with a history of uterine cervical cancer than in those with a history of thyroid cancer. In contrast, subjects with a history of uterine cervical cancer had significantly lower odds of developing PIH than those with a history of thyroid cancer. Subjects with a history of breast cancer had significantly higher odds of having PTB at less than 37 weeks of gestation than those with a history of thyroid cancer. In subjects with a history of malignant tumors other than uterine cervical, breast, and thyroid cancers, the odds of having PTB at less than 37 and 34 weeks of gestation and LBW infants were significantly higher than those with a history of thyroid cancer. In contrast, subjects with a history of malignant tumors other than uterine cervical, breast, and thyroid cancers had significantly lower odds of developing fetal anomalies in singleton pregnancies than those with a history of thyroid cancer. Differences in the prevalence of multiple pregnancies, miscarriages, GDM, and placenta previa or low-lying placenta among

TABLE 3 Differences in the pregnancy outcomes among types of malignant tumor

Pregnancy outcomes	Type of malignant tumor			
	History of cervical cancer	History of breast cancer	History of thyroid cancer	History of malignant tumor other than cervical, breast, and thyroid cancer
Multiple pregnancies, case/*n* (%)	7/455 (1.5)	4/342 (1.2)	6/341 (1.8)	9/808 (1.1)
Model 1, OR (95% CI)	0.88 (0.29–2.65)	0.66 (0.19–2.38)	Reference	0.63 (0.22–1.79)
Model 2, OR (95% CI)[a]	0.81 (0.26–2.50)	0.56 (0.15–2.06)	Reference	0.67 (0.23–1.93)
Miscarriage, case/*n* (%)	8/455 (1.8)	7/342 (2.1)	5/341 (1.5)	10/808 (1.2)
Model 1, OR (95% CI)	1.21 (0.39–3.78)	1.38 (0.43–4.41)	Reference	0.83 (0.28–2.47)
Model 2, OR (95% CI)[b]	1.12 (0.35–3.55)	1.18 (0.36–3.84)	Reference	0.89 (0.30–2.65)
Preterm birth at less than 37 weeks of gestation, case/*n* (%)	137/449 (30.5)	44/333 (13.2)	25/333 (7.5)	112/791 (14.6)
Model 1, OR (95% CI)	5.39 (3.34–8.70)	1.85 (1.09–3.13)	Reference	2.01 (1.26–3.20)
Model 2, OR (95% CI)[b]	5.42 (3.34–8.78)	1.87 (1.09–3.19)	Reference	2.01 (1.26–3.22)
Preterm birth at less than 34 weeks of gestation, case/*n* (%)	67/449 (14.9)	11/333 (3.3)	8/333 (2.4)	44/791 (5.6)
Model 1, OR (95% CI)	7.03 (3.27–15.1)	1.39 (0.55–3.51)	Reference	2.31 (1.07–5.01)
Model 2, OR (95% CI)[b]	6.81 (3.16–14.7)	1.47 (0.58–3.77)	Reference	2.24 (1.03–4.86)
Preterm birth at less than 32 weeks of gestation, case/*n* (%)	42/449 (9.4)	7/333 (2.1)	8/333 (2.4)	25/791 (3.2)
Model 1, OR (95% CI)	4.09 (1.86–8.96)	0.87 (0.31–2.43)	Reference	1.32 (0.59–2.97)
Model 2, OR (95% CI)[b]	3.84 (1.75–8.44)	0.90 (0.32–2.55)	Reference	1.27 (0.56–2.87)
Pregnancy induced hypertension, case/*n* (%)	15/449 (3.3)	17/333 (5.1)	23/333 (6.9)	42/791 (5.3)
Model 1, OR (95% CI)	0.47 (0.24–0.91)	0.73 (0.38–1.38)	Reference	0.76 (0.45–1.28)
Model 2, OR (95% CI)[b]	0.44 (0.22–0.86)	0.57 (0.29–1.10)	Reference	0.82 (0.48–1.41)
Gestational diabetes mellitus, case/*n* (%)	31/449 (6.9)	17/333 (5.1)	19/333 (5.7)	46/791 (5.8)
Model 1, OR (95% CI)	1.09 (0.59–2.00)	0.87 (0.44–1.72)	Reference	1.04 (0.59–1.81)
Model 2, OR (95% CI)[b]	1.03 (0.55–1.90)	0.71 (0.36–1.42)	Reference	1.10 (0.62–1.93)
Placenta previa or low-lying placenta, case/*n* (%)	8/449 (1.8)	13/333 (3.9)	5/333 (1.5)	21/791 (2.7)
Model 1, OR (95% CI)	1.19 (0.39–3.67)	2.67 (0.94–7.57)	Reference	1.79 (0.67–4.79)
Model 2, OR (95% CI)[b]	1.15 (0.37–3.55)	2.23 (0.78–6.40)	Reference	1.91 (0.71–5.14)
Fetal anomalies in singleton pregnancy, case/*n* (%)	9/442 (2.0)	4/329 (1.2)	10/327 (3.1)	7/782 (0.9)
Model 1, OR (95% CI)	0.66 (0.27–1.64)	0.39 (0.12–1.26)	Reference	0.29 (0.11–0.76)
Model 2, OR (95% CI)[a]	0.68 (0.27–1.70)	0.37 (0.11–1.23)	Reference	0.30 (0.11–0.79)
Infant birth weight in singleton pregnancies, gram				
Model 1, Estimate (95% CI)	−266 (−351 to −181)	12 (−76 to 100)	Reference	−41 (−116 to 33)
Model 2, Estimate (95% CI)[a]	−265 (−350 to −180)	11 (−79 to 100)	Reference	−39 (−114 to 36)
Low birth weight infant in singleton pregnancies, case/*n* (%)	130/30.4 (30.4)	43/319 (13.5)	38/313 (12.1)	135/763 (17.7)
Model 1, OR (95% CI)	3.13 (2.08–4.71)	1.10 (0.69–1.76)	Reference	1.54 (1.04–2.28)
Model 2, OR (95% CI)[a]	3.09 (2.05–4.66)	1.10 (0.68–1.77)	Reference	1.52 (1.02–2.25)

Model 1: Medical institutions were included as random intercepts in the model.; [a]Adjusted for maternal age when gestational sac was confirmed (≥ 35 years or not) and conception method (spontaneous pregnancy, non-ART, or ART). Medical institutions were included as random intercepts in the model.; [b]Adjusted for maternal age when gestational sac was confirmed (≥ 35 years or not), multiple pregnancies, and conception method (spontaneous pregnancy, non-ART, or ART). Medical institutions were included as random intercepts in the model. and Abbreviations: ART, assisted reproductive technology; CI, confidence interval; OR, odds ratio.

patients with a history of malignant tumor were not statistically significant.

Discussion

To the best of our knowledge, this study is the largest case-based analysis of perinatal data among cancer survivors of CAYA generation in Japan. This study revealed that the prevalence of PTB is high among cancer survivors in Japan. According to the Maternal and Child Health Statistics in Japan,[19] the percentage of PTB for singleton deliveries in Japan since 2010 ranged from 5.6% to 5.7%, and the prevalence of LBW ranged from 8.1% to 8.4%. In this study, the proportion of PTB was 16.0% and that of LBW was 18.5% in cancer survivors, which were clearly more frequent. The high prevalence of PTB is in line with the previous studies.[4–6,9] The perinatal outcomes of childhood cancer survivors in Japan reported a high incidence of PTB in pregnancies after radiotherapy.[15] The risk of PTB increases only after high doses of uterine radiation.[9] Although the mechanism is unknown, some reports suggest that abdominal irradiation reduces uterine volume, hormone replacement therapy does not provide sufficient endometrial growth, and uterine blood flow decreases.[20,21]

This study also clarified the differences in pregnancy outcomes among patients with a history of malignant tumors. For uterine cervical cancer, the risk of PTB was high. A possible reason for this is that uterine cervical cancer survivors underwent conization or radical trachelectomy (no detailed data on surgery was available in this study). It has been reported that the percentage of PTB is significantly higher in survivors of uterine cervical cancer than the control group during pregnancy after conization, and that of late miscarriage, premature rupture of membranes (PROM), cesarean delivery, and LBW infants is increased.[22,23] In addition, the percentage of PTB has been shown to be high (25%–28%) in pregnancy after radical trachelectomy.[24,25] As a mechanism of PTB, a shortened cervix is thought to lead to a loss of mechanical, biochemical, and immunological barriers resulting in cervical incompetence, ascending infection, higher risk of miscarriages, preterm PROM, and chorioamnionitis.[26]

The risk of PTB was also found to be higher in breast cancer and malignant tumor survivors than in uterine cervical, breast, and thyroid cancer survivors. For breast cancer survivors, several retrospective cohort studies have reported an association with PTB.[27,28] The breast cancer survivors in this study showed a high frequency of conception on ART (17.7%), which might affect the risk of PTB. In addition, breast cancer survivors were older compared to other cancer survivors in this study (the gestational sac was confirmed at age >35 years: 76.7%). Statistically, the effect of maternal age was adjusted, but there may be an effect of factors affecting PTB, such as myoma and fetal abnormalities associated with maternal age advancement. In Japan, pre-treatment cryopreservation of cancer survivors was found to be the most common practice among breast cancer patients, according to a questionnaire in this study.[29] The impact of cancer treatment and ART methods should be evaluated comprehensively, especially among breast cancer survivors.

The prevalence of LBW infants was high in this study. This result is in line with the results of previous studies reporting a likelihood of cancer survivors giving birth to LBW infants.[4,6,9] This result may be associated with the high prevalence of preterm births in this study. In addition, a meta-analysis reported that the risk of small-for-gestational-age (SGA) deliveries is not high, suggesting that fetal growth restriction might not be associated with cancer survivors.[9]

The prevalence of PIH, GDM, placenta previa or low-lying placenta, multiple pregnancies, miscarriages, and malformations showed no remarkable differences between our study subjects and the general Japanese population. Most of the past literature in Japan also reported that the prevalence of maternal complications, including PIH and GDM, is less common compared the general prevalence.[30–32] It is unclear why the maternal complications are less frequent in this study population, as compared to the general population.

In this study, the proportion of women aged 15–24, 25–29, 30–34, 35–39, and >40 years when the gestational sac was confirmed was 3.6%, 14.4%, 30.2%, 36.5%, and 11.8%, respectively. According to the Maternal and Child Health Statistics in Japan,[19] which reflects the Japanese general population, the proportion of women aged 15–24, 25–29, 30–34, 35–39, and >40 years at the time of delivery was 9.4%, 25.5%, 36.5%, 22.9%, and 5.7%, respectively. Therefore, these results suggest advanced maternal age at delivery in the cancer survivors compared with the general population.

The strength of this study is that it is the first large-scale study of pregnancy outcomes among female cancer survivors of the CAYA generation, particularly

AYA generation in Japan. However, there are some limitations to this study. First, we did not assess pregnant women with no history of cancer as controls. Second, maternal body mass index, gestational weight gain, parity, smoking status during pregnancy, and infant sex were not assessed in this study. Therefore, it was not possible to consider the association of these factors with SGA births. Finally, with regard to the method of treatment, detailed data on surgery, chemotherapy, radiation, and hormone therapy are not available, and it is also unclear whether the treatment methods were used alone or in combination. Moreover, the sample size was too small to sufficiently analyze patients with a history of some types of malignancies. However, we considered it necessary to analyze perinatal outcomes by classifying the primary cancer site. Therefore, the history of malignant tumors was sorted into the top three types and other types in descending order of frequency (i.e., uterine cervical cancer, breast cancer, thyroid cancer, and malignant tumors other than uterine cervical, breast, and thyroid cancers) The third most common malignant tumor (i.e., thyroid cancer) in this study was set as the reference category.

In conclusion, the analysis of pregnancies of CAYA cancer survivors showed that there was a trend toward advanced maternal age, and uterine cervical, breast, and thyroid cancers were the most common cancer types in this group of women. As for the adverse pregnancy outcomes, PTB and LBW tended to be more frequent among cancer survivors. The increased likelihood of adverse pregnancy outcomes should be considered by healthcare providers when planning counseling and perinatal care for cancer survivors. A nationwide study is required for a detailed assessment of pregnancy outcomes in Japanese cancer survivors.

Acknowledgments

We express our appreciation to all the clinicians who participated in this study. This study was supported by a grant (18ck0106230h0003) from the Japan Agency for Medical Research and Development and by MHLW Research for Promotion of Cancer Control Program Grant Number JPMH19EA1015.

Conflict of Interest

None declared.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1: supporting information

Figure S1 Flow chart