Adverse pregnancy outcomes of cancer survivors and infectious disease in their infants: The Japan Environment and Children's Study

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Abstract. Birth cohort studies examining pregnancy and infant outcomes among adolescent and young adult (AYA) cancer survivors have been limited. The present study examined whether AYA cancer affects pregnancy outcomes of survivors and infectious diseases in their infants up to 1 year of age. Pregnant women were recruited for the Japan Environment and Children's Study, a nationwide, large-scale, prospective cohort study. The present study included 103,060 pregnant women and collected questionnaire-based data during the first and second/third trimester, and at 1 month, 6 months and 1 year after delivery. Adverse pregnancy outcomes and infectious diseases in infants up to 1 year of age were compared between AYA cancer survivors and pregnant women without a history of cancer using binominal logistic regression analyses and a multiple imputation method. Of 99,816 participants (3,244 were missing), 1,102 (1.1%) had a cancer history, including 812 participants (0.8%) with a history of cervical cancer. Among cervical cancer survivors, the adjusted (a)ORs were as follows: 3.25 (95% CI, 2.31-4.57; q=0.00) for a preterm birth <34 weeks' gestation; 2.82 (95% CI, 2.31-3.44; q=0.00) for a preterm birth <37 weeks' gestation; and 1.67 (95% CI, 1.36-2.06; q=0.00) for premature rupture of the membrane. Among the other cancer survivors, the aOR for caesarean section was 1.43 (95% CI, 1.10-1.87; q=0.0). Furthermore, lower respiratory tract inflammation in 1-year-old infants born by vaginal delivery increased significantly in cases with a history of cervical cancer (aOR, 1.77; 95% CI, 1.33-2.36; q=0.00). The present study identified the risk of lower respiratory tract inflammation in 1-year-old infants born by vaginal delivery in cervical cancer survivors for the first time. In addition, the frequency of caesarean section increased in all cancer survivors. No risk of congenital anomalies or other infections were found in the total group of cancer survivors.

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Introduction

Adolescent and young adult (AYA) patients with cancer have become long-term survivors because of improvements in early diagnosis and treatment. Five-year relative survival rates of over 80% have been estimated for the AYA cancer population in the United States (1). Cancer survivors were found to have fewer pregnancies across all cancer types, and the chance of achieving a first pregnancy was also lower with the use of chemotherapy (2-4).

Chow *et al* conducted a study of 10,938 survivors and 3,949 siblings (2); 38% of survivors and 62% of siblings reported having or siring a pregnancy and 83 and 90% of these individuals reported at least one livebirth, respectively. Multivariable analysis showed a decreased likelihood of siring or having a pregnancy (male survivors: hazard ratio 0.63, 95% CI 0.58-0.68; female survivors: 0.87, 0.81-0.94) or of having a livebirth (male survivors: 0.63, 0.58-0.69; female survivors: 0.82, 0.76-0.89). A recent population-based cohort study using universal health care databases in Ontario, Canada compared 14,316 AYA cancer survivors and 60,975 unexposed women (4). The overall risk of an infertility diagnosis was higher in cancer survivors (relative risk 1.30, 95% CI 1.23-1.37). Among females with brain, breast, thyroid or colorectal cancer, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, or melanoma, those with breast or thyroid cancer, hematological malignancies, or melanoma have a higher risk of a subsequent infertility diagnosis.

Several studies concerning birth outcomes among AYA cancer survivors have been reported (1,2,5,6). Anderson *et al* conducted a survey using the North Carolina Central Cancer Registry from January 2000 to December 2013, to examine 2,598 births to AYA cancer survivors and found that the

survivors had a significantly increased prevalence of preterm birth, low birth weight, and caesarean delivery, but not small-for-gestational-age (SGA) birth or low Apgar score (<7) relative to the comparison cohort of 1,299 (1).

Regarding uterine cervical cancer, about 10,000 women suffer from and 3,000 die from it recent every year and the peak of onset is in the 30s in Japan. Patients with cervical cancer increased year by year (7). The current human papilloma virus (HPV) vaccine can prevent 60~70% of cervical cancers, and the WHO has confirmed its efficacy and safety. Even in developed countries in Europe and the United States and Japan, vaccination has shown that HPV infection rates and the frequency of precancerous lesions are reduced compared to those who have not been vaccinated. In Japan, the HPV vaccine has been routinely administered since April 2013, but due to reports about severe symptoms after vaccination, active encouragement by the Ministry of Health, Labour and Welfare has been refrained between June 2013 and November 2021. Cervical cancer must be included as AYA cancer because it is the second most common cancer after breast cancer in 20-39 year olds of Japanese population.

However, birth cohort studies examining pregnancy and perinatal outcomes among AYA cancer survivors with adjustment of appropriate covariates using multiple imputation have been limited. We focused on not only pregnancy outcomes but also infant outcomes because there has been no birth cohort study that included infant outcomes up to age of one year.

This study aimed to examine the outcomes of pregnancy and the postpartum period up to the age of one year in cancer survivors using data obtained from the Japan Environment and Children's Study (JECS).

Materials and methods

Study design. In the JECS, pregnant women were recruited between January, 2011 and March, 2014. Eligibility criteria for expectant mothers were as follows: that they i) resided at the time of recruitment in any of the study areas selected by 15 Regional JECS Centers located countrywide; ii) had an expected delivery date after August 1, 2011; and iii) were capable of comprehending the Japanese language and completing the self-administered questionnaire (8-12). Those residing outside the study areas, even if they visit the cooperating health care providers within the study areas, were excluded from the study. Excluded were those who did not consent to the study protocol and could not be accessed during the pregnancy period. The participants were able to withdraw from the study at any time.

The sample size has been calculated in the JECS protocol. In principle, women completed the questionnaires during the first and the second/third trimester, and at one month, six months and one year after delivery. Their medical records were transcribed by physicians, midwives/nurses, and/or trained Research Co-coordinators at registration, just after delivery and at one month after delivery.

The present study was based on the jecs-ta-20190930 data set, which includes 104,062 registered children (fetuses and embryos), and was released restrictively to all concerned in October, 2019. The second and third children of multiple pregnancies were excluded and these numbered 1,002 (0.96%, Fig. 1). Finally, 103,060 pregnancies were included in the main analysis. The mean (SD) age and gestational weeks at registration was 30.7 (5.1) and 14.2 (6.4) weeks. Regarding children, just 100,143 children were included in the main analysis because 2,917 children with indeterminate or missing sex whose sex were not ascertained because of immaturity or congenital anomalies were excluded (Fig. 1). The JECS population has been recognized as representative of pregnant women in Japan (11).

The JECS was approved by the Institutional Review Board of the Japan National Institute for Environmental Studies (approval no. 100910001), as well as by the ethics committees of all participating institutions. This study was conducted with the approval of the Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences (approval nos. 554 and 554-2). Written informed consent was obtained from all participants.

Data collection. The first questionnaire included sociodemographic characteristics, medical histories, details of all previous pregnancies and exercise habits. The socioeconomic status was assessed by the education level and annual household income and lifestyle details were included in the second questionnaire.

The first medical record transcript included maternal age, gestational weeks at registration, maternal body weight, height, conception, and details of all previous pregnancies (vaginal delivery/caesarian delivery/miscarriage/induced abortion/stillbirth).

The medical record transcript at delivery included maternal age, gestational weeks at miscarriage and delivery, single/multiple pregnancies, live birth/stillbirth, miscarriage/induced abortion, male/female, birth weight, vaginal/caesarian delivery, pregnancy complications and perinatal outcome.

The questionnaire at six months and one year after birth included the presence/absence of infectious disease in the infant and vaccination.

Outcomes. The maternal and neonatal outcomes of interest were preterm birth, placenta previa, premature rupture of the membrane (PROM), oligohydraminios, hypertensive disorders of pregnancy (HDP), uterine infection, SGA <10th percentile, congenital anomalies and caesarean section.

The infant outcomes were upper respiratory tract inflammation and respiratory syncytial (RS) virus infection at six months and otitis media, upper and lower respiratory tract inflammation, diarrhea and vomiting, influenza, exanthema subitum, herpangina, hand, foot and mouth disease, adenovirus, RS virus infection and chickenpox at one year.

Exposures and covariates. Exposures included a history of cervical cancer and other cancers. Potential covariates for maternal and neonatal outcomes were maternal age at registration (<20, 20-29, 30-39, ≥40 years), body mass index (BMI, <18.5, 18.5-25.0, ≥25.0), smoking status, income level per year [<2, 2-<4, 4-<6, 6-<8, 8-<10, ≥10 JPYx 1 million, (1 US$=114.38 JPY, 21 October 2021)], pregnancy loss history, the presence/absence of in vitro fertilization and embryo transfer (IVF-ET), and the presence/absence of previous deliveries.

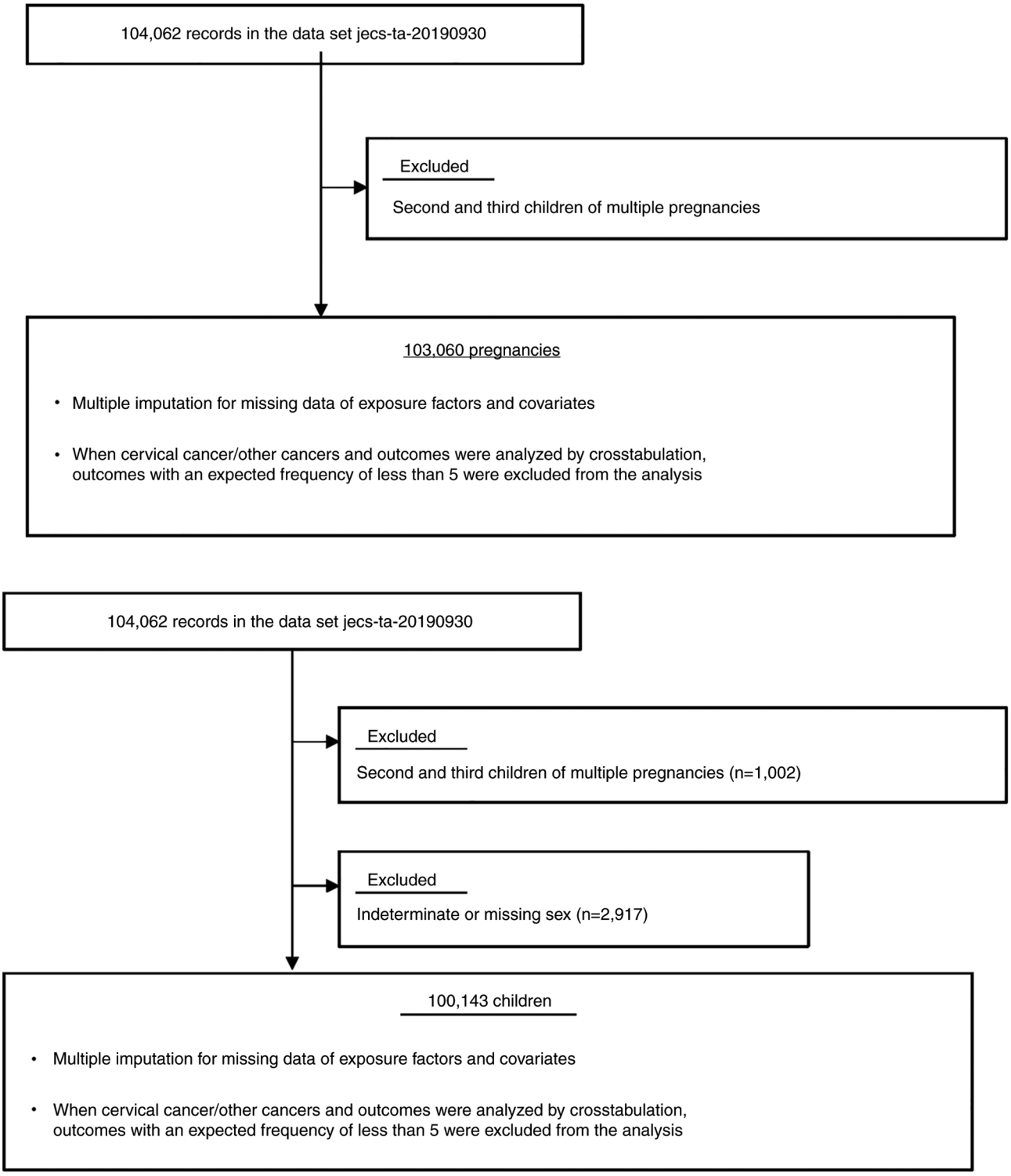

Figure 1. Flow diagram of the present study. The first flow chart shows the mothers and the second flow chart shows the infants.

Covariates for six months were maternal age at registration, maternal BMI before pregnancy, maternal smoking status, household income, pregnancy loss history, the presence/absence of IVF-ET, the presence/absence of previous deliveries, sex of the child, maternal allergy and ear, nose, and throat disease, congenital diseases of the child, feeding method at one month of age, the number of family members living with the child, the month of questionnaire entry at six months of age, the period of breast milk intake (until six month of age), the period of artificial nutrition intake (until six months), attendance at a nursery facility (at six months), influenza virus vaccination, rotavirus vaccination, and Haemophilus influenzae type b (Hib) and pneumococcal vaccination.

To covariates at one year, we added the month of questionnaire entry at one year, the period of breast milk intake (until one year), the period of artificial nutrition intake (until one year), attendance at a nursery facility (at one year), maternal working pattern, influenza virus vaccination, rotavirus

vaccination, Hib and pneumococcal vaccination, palivizumab injection, and chickenpox vaccination to the covariates for six-months of age.

Statistical analysis. The maternal and infant demographic characteristics of the participants were shown in relation to discrete data. χ^2 tests were performed to compare the association between the history of cancer and each variable shown as nominal variables. One-way ANOVA was performed when we compared mean values between the history of cancer and each variable shown as numerical variables. If we would obtain significant ANOVA results, Tukey's pairwise post hoc tests between variables were conducted. Binominal logistic regression analyses were performed by adding all the covariates to calculate the adjusted ORs (aORs) for association between the history of cancer and each outcome. Traditionally, univariate analyses were performed first to find out the significant confounders for adjusting confounding effect for subsequent multivariate analysis. As explained by Vandenbroucke *et al*, such procedure is not recommended now (13). Significance tests of univariate analysis should be avoided as a criterion for selecting confounders to adjust for. The STROBE statement gives that P-values are not an appropriate criterion for selecting which confounders to adjust for in analysis; even small differences in a confounder that has a strong effect on the outcome can be important.

Since missing data can potentially undermine the scientific credibility of causal conclusions, we applied a multiple imputation method to reduce the potential non-response bias created by the missing data and to improve the precision of the estimates when calculating the aORs. When cervical cancer/other cancers and outcomes were analyzed by cross-tabulation, outcomes with an expected frequency of less than 5 were excluded from the analysis. To prevent multiple comparisons possibly yielding false positive findings, we adopted the Benjamini-Hochberg method and assessed statistical significance by obtaining the q-values adjusted for a false discovery rate.

χ^2 test was performed to compare the association between the mode of delivery and each variable and Student's t-tests were used for analyzing mean data.

All calculations were conducted using SPSS version 26 (IBM Corp., Japan), and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Of 99,816 participants (3,244 were missing), 1,102 (1.1%) had a cancer history including 56 patients with cancer during pregnancy (Table I). Of these, 812 participants (0.8%) had a history of cervical cancer and 290 (0.3%) had other cancers. Fifty seven (0.057%) had breast cancer, 8 (0.008%) had endometrial cancer, 4 (0.004%) had stomach cancer, 11 (0.01%) had colon cancer, 40 (0.04%) had a blood cancer, and 176 (0.17%) had other cancers.

Characteristics of the 99,816 pregnant women are shown in Table I. Maternal age, smoking status, income level, pregnancy loss history, the presence/absence of IVF-ET, previous deliveries, and employment status were significantly associated with cervical cancer, other cancers and no history of any cancer. These variables were analyzed for covariates of maternal outcomes.

Characteristics of the 99,816 infants and the association between each variable and the cancer history are shown in Table II. The period of both breast milk and artificial nutrition intake (both in months until six months and one year of age) and palivizumab injection at one year of age were significantly associated among three groups. These variables were analyzed for covariates of infant outcomes.

Cervical cancer, blood cancer and other cancers were associated with caesarean section (Table SI). Maternal age, BMI, smoking status, income, the number of previous pregnancy losses, the presence of IVF-ET, the month of the questionnaire entry at six months and one year of age were also associated with caesarean section.

Feeding by infant formula at one month, a short period of breast feeding and a long period of artificial nutrition until six months and one year, and a palivizumab injection were associated with caesarean section (Table SII).

Among the 812 women with a history of cervical cancer, a preterm birth at both <34 and 37 weeks' gestation and PROM increased significantly (Table III). aORs using multiple imputation were as follows: 3.25 (95% CI, 2.31 to 4.57, q=0.00) for preterm birth <34 weeks' gestation, 2.82 (2.31 to 3.44, q=0.00) for preterm birth <37 weeks' gestation, and 1.67 (1.36 to 2.06, q=0.00) for PROM. History of cervical cancer did not increase the risk of congenital anomalies.

In the 290 women with a history of other cancers, the incidence of caesarean section was significantly higher (1.43, 1.10 to 1.17, q=0.04).

The associations of infant outcomes with maternal cancer histories are shown in Table IV. Lower respiratory tract inflammation in one-year-old infants born by vaginal delivery, but not caesarean section, increased significantly in cases with a history of cervical cancer (1.77, 1.33 to 2.36, q=0.00).

Discussion

We found for the first time that lower respiratory tract inflammation in one-year-old infants born by vaginal delivery but not caesarean section was significantly higher in cervical cancer survivors. No risk of other infant inflammations was found in any of the cancer survivors.

Newborn babies experience rapid colonization mainly by passage through the maternal vagina, and the difference in the gut microbiota of infants between vaginal delivery and caesarean section may result from significant differences between vaginal and endometrial microbiota (14). Shao *et al* conducted a whole-genome shotgun metagenomic analysis of 1,679 gut microbiota samples during the neonatal period and in infancy from 596 full-term babies born in UK hospitals and found disrupted transmission of maternal Bacteroides strains, and high-level colonization by opportunistic pathogens associated with the hospital environment (including *Enterococcus, Enterobacter* and *Klebsiella species*), in babies delivered by caesarean section (15). These effects were also seen in vaginally delivered babies whose mothers underwent antibiotic prophylaxis and in babies who were not breastfed during the neonatal period. This analysis demonstrated that the mode of delivery is a significant factor that affects the composition of

Table I. Demographic characteristics of mothers.

Variable	Total n=99,816 n (%)	History of cancer			P-value[c]
		Cervical[a] n=812 n (%)	Others[b] n=290 n (%)	Nothing n=98,714 n (%)	
Age, years					<0.001
<20	1,145 (1.1)	6 (0.7)	0 (0.0)	1139 (1.2)	
20-29	39,814 (39.9)	249 (30.7)	66 (22.8)	39,499 (40.0)	
30-39	55,278 (55.4)	518 (63.8)	195 (67.2)	54,565 (55.3)	
≥40	3,500 (3.5)	39 (4.8)	29 (10.0)	3,432 (3.5)	
Missing	79 (0.1)	0 (0.0)	0 (0.0)	79 (0.1)	
Pregnancy body mass index, kg/m^2					0.203
<18.5	16,147 (16.2)	150 (18.5)	45 (15.5)	15,952 (16.2)	
18.5-24.9	72,897 (73.0)	564 (69.5)	217 (74.8)	72,116 (73.1)	
≥25.0	10,724 (10.7)	98 (12.1)	28 (9.7)	10,598 (10.7)	
Missing	48 (0.0)	0 (0.0)	0 (0.0)	48 (0.0)	
Smoking status					<0.001
Never smoker	55,891 (56.0)	301 (37.1)	169 (58.3)	55,421 (56.1)	
Ex-smoker, stopped before learning of pregnancy	23,162 (23.2)	262 (32.3)	73 (25.2)	22,827 (23.1)	
Ex-smoker, stopped on awareness of pregnancy	13,258 (13.3)	153 (18.8)	32 (11.0)	13,073 (13.2)	
Current smoker	4,429 (4.4)	72 (8.9)	6 (2.1)	4,351 (4.4)	
Missing	3,076 (3.1)	24 (3.0)	10 (3.4)	3,042 (3.1)	
Annual household income, one million Japanese yen					0.018
<2	5,132 (5.1)	63 (7.8)	10 (3.4)	5,059 (5.1)	
2-<4	31,324 (31.4)	272 (33.5)	80 (27.6)	30,972 (31.4)	
4-<6	29,957 (30.0)	228 (28.1)	91 (31.4)	29,638 (30.0)	
6-<8	14,409 (14.4)	114 (14.0)	53 (18.3)	14,242 (14.4)	
8-<10	5,913 (5.9)	44 (5.4)	22 (7.6)	5,847 (5.9)	
≥10	3,873 (3.9)	26 (3.2)	11 (3.8)	3,836 (3.9)	
Missing	9,208 (9.2)	65 (8.0)	23 (7.9)	9,120 (9.2)	
Pregnancy loss history					<0.001
0	76,245 (76.4)	576 (70.9)	216 (74.5)	75,453 (76.4)	
1	17,572 (17.6)	163 (20.1)	53 (18.3)	17,356 (17.6)	
2	3,891 (3.9)	38 (4.7)	14 (4.8)	3,839 (3.9)	
≥3	1,135 (1.1)	21 (2.6)	1 (0.3)	1,113 (1.1)	
Missing	973 (1.0)	14 (1.7)	6 (2.1)	953 (1.0)	
In vitro fertilization and embryo transfer					<0.001
No	96,639 (96.8)	763 (94.0)	268 (92.4)	95,608 (96.9)	
Yes	3,177 (3.2)	49 (6.0)	22 (7.6)	3,106 (3.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Previous live birth					0.018
No	39,299 (39.4)	286 (35.2)	116 (40.0)	38,897 (39.4)	
Yes	58,116 (58.2)	519 (63.9)	163 (56.2)	57,434 (58.2)	
Missing	2,401 (2.4)	7 (0.9)	11 (3.8)	2,383 (2.4)	
Maternal allergy and ear, nose, and throat disease					0.040
No	42,109 (42.2)	343 (42.2)	101 (34.8)	41,665 (42.2)	
Yes	57,707 (57.8)	469 (57.8)	189 (65.2)	57,049 (57.8)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
The month of questionnaire entry at 6 months of age					0.963
Spring (March to May)	25,016 (25.1)	203 (25.0)	67 (23.1)	24,746 (25.1)	
Summer (June to August)	21,339 (21.4)	174 (21.4)	63 (21.7)	21,102 (21.4)	
Autumn (September to November)	20,777 (20.8)	157 (19.3)	63 (21.7)	20,557 (20.8)	
Winter (December to February)	24,844 (24.9)	206 (25.4)	73 (25.2)	24,565 (24.9)	
Missing	7,840 (7.9)	72 (8.9)	24 (8.3)	7,744 (7.8)	

Table I. Continued.

Variable	Total n=99,816 n (%)	History of cancer: Cervical[a] n=812 n (%)	History of cancer: Others[b] n=290 n (%)	History of cancer: Nothing n=98,714 n (%)	P-value[c]
The month of questionnaire entry at 1 year of age					0.950
Spring (March to May)	20,467 (20.5)	166 (20.4)	59 (20.3)	20,242 (20.5)	
Summer (June to August)	23,897 (23.9)	203 (25.0)	65 (22.4)	23,629 (23.9)	
Autumn (September to November)	24,319 (24.4)	184 (22.7)	66 (22.8)	24,069 (24.4)	
Winter (December to February)	20,434 (20.5)	159 (19.6)	58 (20.0)	20,217 (20.5)	
Missing	10,699 (10.7)	100 (12.3)	42 (14.5)	10,557 (10.7)	
Current employment status (when the child is 1-year-old)					<0.001
Full-time homemaker	42,464 (42.5)	366 (45.1)	122 (42.1)	41,976 (42.5)	
Unemployed	3,231 (3.2)	30 (3.7)	7 (2.4)	3,194 (3.2)	
Student	202 (0.2)	2 (0.2)	1 (0.3)	199 (0.2)	
Full-time employee	24,578 (24.6)	143 (17.6)	69 (23.8)	24,366 (24.7)	
Part-time employee	12,294 (12.3)	105 (12.9)	25 (8.6)	12,164 (12.3)	
Self-employed	3,238 (3.2)	46 (5.7)	15 (5.2)	3,177 (3.2)	
Part time work at home	600 (0.6)	5 (0.6)	0 (0.0)	595 (0.6)	
Other	1,235 (1.2)	8 (1.0)	3 (1.0)	1,224 (1.2)	
Missing	11,974 (12.0)	107 (13.2)	48 (16.6)	11,819 (12.0)	

[a]Of 812 mothers, four had a history of other cancers; [b]Four mothers who also had cervical cancer were excluded; [c]χ^2 tests were performed.

the gut microbiota throughout the neonatal period and into infancy.

A meta-analysis revealed that caesarean section is a risk factor for respiratory tract infections (pooled OR 1.30, 95% CI 1.06-1.60), asthma (1.23, 1.14-1.33) as well as obesity (1.35, 1.29-1.41) in offspring (16). The risk of severe lower respiratory inflammation during infancy was moderately elevated in infants born by planned caesarean, compared to those born vaginally, in the general population (17). Thus, rapid colonization by maternal vaginal microbiota might be important for protecting the infant from infectious disease.

In the present study however, lower respiratory tract inflammation was higher in infants born by vaginal delivery from cervical cancer survivors. Cervical cancer is well-known to be caused by high-risk human papillomavirus (HPV) infections. HPV infection induces vaginal microbial taxonomic shifts and may influence the maintenance of microbial homeostasis (18). Sims *et al* demonstrated that the diversity of gut microbiota was associated with a favorable response to chemoradiation in patients with cervical cancer and that compositional variation correlated with short term and long-term survival (19).

Regarding advance pregnancy outcomes in AYA cancer survivors, the first birth cohort study compared outcomes of 1,894 AYA survivors diagnosed in Western Australia during the period from 1982 to 2007 with those of controls matched by maternal age, parity and year of delivery (5). Female survivors had an increased risk of threatened abortion, gestational diabetes, pre-eclampsia, post-partum hemorrhage, caesarean delivery, maternal postpartum hospitalization >5 days, premature birth (<37 weeks), low birth weight, fetal growth restriction, neonatal distress indicated by low Apgar score (<7) at 1 min, and the need for resuscitation or special care nursery admission. Our present study found no risk of HDP and SGA. The limitation of Haggar's study was that covariates were adjusted for only age and parity (5).

Anderson *et al* showed a significantly increased risk of preterm birth (prevalence ratio 1.52, 95% CI 1.34-1.71), low birth weight (1.59, 1.38-1.83), and caesarean delivery (1.08, 1.01-1.14) (1). The higher prevalence of these outcomes was most concentrated among births to women diagnosed during pregnancy. Other factors associated with a preterm birth and low birth weight included treatment with chemotherapy and a diagnosis of breast cancer, non-Hodgkin's lymphoma, or gynecological cancers. The prevalence of SGA and a low Apgar score (<7) did not differ significantly between groups. The results were in line with our findings.

Ji *et al* found a risk of stillbirth among children of female cancer survivors who were born within three years after a cancer diagnosis (1.92, 1.03-3.57) and suggested that the risk of stillbirth was negatively associated with the time after the diagnosis, providing evidence that the adverse effect associated with cancer treatment may diminish with time (20).

Cervical cancer was the most frequent and women with a prior cervical cancer had a higher risk of preterm birth in the present study. This is in line with previous study (21,22). Nitecki *et al* found that 2.9% (118/4087) of patients conceived at least 3 months after fertility-sparing surgery for stage I cervical cancer and had higher odds of preterm birth and

Table II. Demographic characteristics of infants.

Variable	Total n=98,627 n (%)	History of cancer			P-value
		Cervical[a] n=804 n (%)	Others[b] n=282 n (%)	Nothing n=97,541 n (%)	
Sex					0.593[c]
Male	50,620 (51.3)	399 (49.6)	142 (50.4)	50,079 (51.3)	
Female	48,007 (48.7)	405 (50.4)	140 (49.6)	47,462 (48.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Congenital diseases					0.427[c]
No	86,507 (87.7)	687 (85.4)	249 (88.3)	85,571 (87.7)	
Yes	8,877 (9.0)	82 (10.2)	25 (8.9)	8,770 (9.0)	
Missing	3,243 (3.3)	35 (4.4)	8 (2.8)	3,200 (3.3)	
Feeding method at 1 month					0.056[c]
Breastfeeding only	40,449 (41.0)	311 (38.7)	96 (34.0)	40,042 (41.1)	
Mixed feeding	54,159 (54.9)	447 (55.6)	177 (62.8)	53,535 (54.9)	
Infant formula only	1,427 (1.4)	16 (2.0)	4 (1.4)	1,407 (1.4)	
Missing	2,592 (2.6)	30 (3.7)	5 (1.8)	2,557 (2.6)	
Number of family members currently living together with the child					0.385[c]
0	135 (0.1)	1 (0.1)	1 (0.4)	133 (0.1)	
1	1,598 (1.6)	18 (2.2)	5 (1.8)	1,575 (1.6)	
2	30,683 (31.1)	225 (28.0)	95 (33.7)	30,363 (31.1)	
≥3	59,558 (60.4)	496 (61.7)	165 (58.5)	58,897 (60.4)	
Missing	6,626 (6.7)	64 (8.0)	16 (5.7)	6,546 (6.7)	
The period of breast milk intake, months until 6 months					0.000[d]; 0.000[e]; 0.004[f]; 0.792[g]
Mean ± SD	5.17±1.6	4.94±1.8	4.86±1.9	5.18±1.6	
Missing	6,063	64	16	6,573	
The period of artificial nutrition intake, months until 6 months					0.000[d]; 0.003[e]; 0.002[f]; 0.443[g]
Mean ± SD	2.61±2.6	2.92±2.6)	3.14±2.6	2.61±2.6	
Missing	6,063	64	16	6,573	
Attending a childcare facility at six months, daycare center/nursery					0.060[c]
Yes	6,418 (6.5)	67 (8.3)	15 (5.3)	6,336 (6.5)	
No	85,365 (86.6)	672 (83.6)	250 (88.7)	84,443 (86.6)	
Missing	6,844 (6.9)	65 (8.1)	17 (6.0)	6,762 (6.9)	
Influenza virus vaccination, at 6 months					0.366[c]
No	90,059 (91.3)	730 (90.8)	261 (92.6)	89,068 (91.3)	
Yes	1,915 (1.9)	10 (1.2)	5 (1.8)	1,900 (1.9)	
Missing	6,653 (6.7)	64 (8.0)	16 (5.7)	6,573 (6.7)	
Rotavirus vaccination, at 6 months					0.284[c]
No	52,051 (52.8)	431 (53.6)	140 (49.6)	51,480 (52.8)	
Yes	39,923 (40.5)	309 (38.4)	126 (44.7)	39,488 (40.5)	
Missing	6,653 (6.7)	64 (8.0)	16 (5.7)	6,573 (6.7)	
Haemophilus influenzae type b vaccination, at 6 months					0.625[c]
No	6,032 (6.1)	55 (6.8)	17 (6.0)	5,960 (6.1)	
Yes	85,942 (87.1)	685 (85.2)	249 (88.3)	85,008 (87.2)	
Missing	6,653 (6.7)	64 (8.0)	16 (5.7)	6,573 (6.7)	
Pneumococcal vaccination, at 6 months					0.927[c]
No	6,763 (6.9)	57 (7.1)	19 (6.7)	6,687 (6.9)	

Table II. Continued.

Variable	Total n=98,627 n (%)	History of cancer: Cervical[a] n=804 n (%)	History of cancer: Others[b] n=282 n (%)	History of cancer: Nothing n=97,541 n (%)	P-value
Yes	85,211 (86.4)	683 (85.0)	247 (87.6)	84,281 (86.4)	
Missing	6,653 (6.7)	64 (8.0)	16 (5.7)	6,573 (6.7)	
The period of breast milk intake, months until 1 year					0.000[d]; 0.000[e]; 0.016[f]; 0.991[g]
Mean ± SD	9.35±3.9	8.71±4.2	8.68±4.3	9.36±3.9	
Missing	8,967	92	34	9,386	
The period of artificial nutrition intake, months until 1 year					0.000[d]; 0.001[e]; 0.015[f]; 0.833[g]
Mean ± SD	5.47±5.1	6.14±5.2	6.36±5.3	5.46±5.1	
Missing	8,967	92	34	9,386	
Attendance at a childcare facility at 1 year, daycare center/nursery					0.910[c]
Yes	23,786 (24.1)	193 (24.0)	64 (22.7)	23,529 (24.1)	
No	64,937 (65.8)	514 (63.9)	183 (64.9)	64,240 (65.9)	
Missing	9,904 (10.0)	97 (12.1)	35 (12.4)	9,772 (10.0)	
Influenza virus vaccination, at 1 year					0.991[c]
No	73,063 (74.1)	583 (72.5)	204 (72.3)	72,276 (74.1)	
Yes	16,052 (16.3)	129 (16.0)	44 (15.6)	15,879 (16.3)	
Missing	9,512 (9.6)	92 (11.4)	34 (12.1)	9,386 (9.6)	
Rotavirus vaccination, at 1 year					0.152[c]
No	50,505 (51.2)	415 (51.6)	127 (45.0)	49,963 (51.2)	
Yes	38,610 (39.1)	297 (36.9)	121 (42.9)	38,192 (39.2)	
Missing	9,512 (9.6)	92 (11.4)	34 (12.1)	9,386 (9.6)	
Haemophilus influenzae type b vaccination, at 1 year					0.238[c]
No	4,520 (4.6)	45 (5.6)	10 (3.5)	4,465 (4.6)	
Yes	84,595 (85.8)	667 (83.0)	238 (84.4)	83,690 (85.8)	
Missing	9,512 (9.6)	92 (11.4)	34 (12.1)	9,386 (9.6)	
Pneumococcal vaccination, at 1 year					0.671[c]
No	6,086 (6.2)	52 (6.5)	14 (5.0)	6,020 (6.2)	
Yes	83,029 (84.2)	660 (82.1)	234 (83.0)	82,135 (84.2)	
Missing	9,512 (9.6)	92 (11.4)	34 (12.1)	9,386 (9.6)	
Chickenpox vaccination, at 1 year					0.928[c]
No	84,793 (86.0)	676 (84.1)	235 (83.3)	83,882 (86.0)	
Yes	4,322 (4.4)	36 (4.5)	13 (4.6)	4,273 (4.4)	
Missing	9,512 (9.6)	92 (11.4)	34 (12.1)	9,386 (9.6)	
Palivizumab injection, at 1 year					<0.001[c]
Yes	2,624 (2.7)	51 (6.3.0)	8 (2.8)	2,565 (2.6)	
No	83,318 (84.5)	632 (78.6)	231 (81.9)	82,455 (84.5)	
Missing	12,685 (12.9)	121 (15.0)	43 (15.2)	12,521 (12.8)	

[a]Of 804 mothers, four had a history of other cancers; [b]Four mothers who also had cervical cancer were excluded; [c]χ^2 tests; [d]One-way ANOVA; [e]Tukey's multiple comparison between Cervical and Nothing categories of the history of cancer; [f]Tukey's multiple comparison between Others and Nothing categories of the history of cancer; [g]Tukey's multiple comparison between Cervical and Others categories of the history of cancer.

neonatal morbidity (21). There was no difference in rates of SGA, stillbirth, caesarean delivery and maternal morbidity. The cervical intraepithelial neoplasia grade 3 (CIN 3) is speculated to be included in the present study because fertility rate after

Table III. The association of maternal and neonatal outcomes with maternal cancer histories.

Maternal and neonatal outcome[b]	History of cervical cancer (n=812)						History of other cancer (n=290)					
	Crude ORs (95% CI)	P-value	Adjusted ORs[c] (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs[c] (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value
Preterm birth <34 weeks' gestation[d]	3.78 (2.69-5.30)	0.00	4.05 (2.81-5.82)	0.00[a]	3.25 (2.31-4.57)	0.00[a]						
Preterm birth <37 weeks' gestation[d]	3.07 (2.52-3.75)	0.00	2.87 (2.31-3.56)	0.00[a]	2.82 (2.31-3.44)	0.00[a]	1.37 (0.87-2.17)	0.17	1.38 (0.85-2.24)	0.53	1.27 (0.81-2.01)	0.53
Placenta previa[d]	1.32 (0.62-2.78)	0.47	1.30 (0.61-2.76)	0.69	1.15 (0.54-2.44)	0.90						
Premature rupture[d]	1.62 (1.32-1.99)	0.00	1.62 (1.30-2.01)	0.00[a]	1.67 (1.36-2.06)	0.00[a]	0.87 (0.56-1.34)	0.52	0.83 (0.52-1.31)	0.67	0.81 (0.52-1.26)	0.58
Oligohydramnios[d]	1.08 (0.59-1.95)	0.81	0.87 (0.43-1.76)	0.94	1.06 (0.58-1.93)	0.97						
Mild hypertensive disorders of pregnancy[d]	0.81 (0.48-1.34)	0.41	0.71 (0.41-1.23)	0.55	0.75 (0.45-1.26)	0.53	1.70 (0.93-3.12)	0.08	1.40 (0.71-2.75)	0.67	1.52 (0.82-2.81)	0.50
Severe hypertensive disorders of pregnancy[d]	1.02 (0.51-2.06)	0.95	0.94 (0.45-2.00)	0.99	0.96 (0.47-1.93)	0.97						
Uterine infection	1.42 (0.67-3.00)	0.36	1.43 (0.63-3.22)	0.67	1.34 (0.63-2.85)	0.69						
Small for gestational age (<10%)[d]	0.73 (0.56-0.95)	0.02	0.74 (0.56-0.97)	0.11	0.73 (0.56-0.95)	0.08	1.02 (0.70-1.50)	0.91	0.99 (0.65-1.50)	1.00	1.02 (0.70-1.51)	0.97
Physical anomalies at birth	1.04 (0.79-1.38)	0.76	1.03 (0.76-1.38)	0.99	1.00 (0.76-1.33)	0.99	1.37 (0.90-2.09)	0.14	1.44 (0.94-2.22)	0.30	1.28 (0.84-1.96)	0.53
Physical anomalies at 1 month	1.16 (0.93-1.47)	0.19	1.10 (0.86-1.40)	0.67	1.14 (0.91-1.44)	0.53	0.98 (0.65-1.48)	0.92	0.96 (0.62-1.48)	0.99	0.94 (0.62-1.41)	0.91
Caesarean	1.32 (1.12-1.55)	0.00	1.25 (1.05-1.49)	0.06	1.19 (1.01-1.41)	0.13	1.64 (1.27-2.13)	0.00	1.44 (1.09-1.91)	0.06	1.43 (1.10-1.87)	0.04[a]

[a]Significance at q<0.05, adjusted using the Benjamin-Hochberg method for false detection rate; [b]outcomes with an expected frequency of less than 5 were excluded from the analysis; [c]Adjusted for maternal age at registration, maternal BMI before pregnancy, maternal smoking status, household income, pregnancy loss history, the presence/absence of IVF-ET, and previous deliveries; [d]Miscarriage and artificial abortion were excluded from analyses.

Table IV. The associations of infant outcomes with maternal cancer histories.

	History of cervical cancer												History of other cancer											
	Transvaginal (n=609)						Caesarean (n=192)						Transvaginal (n=202)						Caesarean (n=80)					
Outcomes[b]	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value
At 6-month-old[c]																								
Otitis media	0.89 (0.50-1.58)	0.70	0.69 (0.35-1.34)	0.89	0.82 (0.46-1.47)	0.95	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Upper respiratory inflammation	1.12 (0.89-1.41)	0.35	1.14 (0.89-1.46)	0.89	1.09 (0.86-1.38)	0.93	1.05 (0.69-1.60)	0.80	0.99 (0.63-1.55)	1.00	0.97 (0.63-1.49)	1.00	1.07 (0.71-1.59)	0.75	0.96 (0.62-1.50)	1.00	1.01 (0.67-1.52)	1.00	1.18 (0.63-2.19)	0.61	1.13 (0.56-2.25)	1.00	1.14 (0.61-2.15)	1.00
Respiratory syncytial virus	0.89 (0.59-1.34)	0.58	0.96 (0.63-1.46)	1.00	0.83 (0.55-1.26)	0.90	1.70 (0.98-2.95)	0.06	1.63 (0.91-2.93)	0.71	1.59 (0.91-2.79)	0.75	0.87 (0.43-1.76)	0.69	1.02 (0.50-2.1)	1.00	0.93 (0.46-1.91)	1.00	-	-	-	-	-	-
Exanthema subitum	1.04 (0.57-1.89)	0.90	0.89 (0.46-1.74)	1.00	0.96 (0.53-1.75)	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Influenza	1.40 (0.77-2.55)	0.27	0.90 (0.42-1.92)	1.00	1.27 (0.69-2.32)	0.93	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea and vomiting (gastroenteritis)	1.58 (0.91-2.74)	0.11	1.57 (0.90-2.76)	0.71	1.36 (0.78-2.38)	0.90	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
At 1-year-old[d]																								
Otitis media	0.91 (0.69-1.20)	0.50	0.83 (0.60-1.15)	0.89	0.89 (0.67-1.18)	0.93	1.10 (0.70-1.73)	0.67	1.11 (0.67-1.83)	1.00	1.05 (0.65-1.68)	1.00	0.83 (0.50-1.37)	0.46	0.88 (0.51-1.53)	1.00	0.87 (0.52-1.45)	1.00	1.24 (0.63-2.42)	0.53	1.89 (0.88-4.02)	0.71	1.45 (0.72-2.92)	0.90
Upper respiratory inflammation	0.99 (0.81-1.22)	0.96	1.10 (0.88-1.38)	0.92	1.02 (0.83-1.25)	1.00	1.31 (0.94-1.82)	0.11	1.08 (0.73-1.59)	1.00	1.31 (0.93-1.85)	0.75	1.27 (0.91-1.77)	0.15	1.22 (0.84-1.75)	0.89	1.22 (0.87-1.71)	0.90	1.80 (1.10-2.93)	0.02	1.77 (0.99-3.16)	0.71	1.72 (1.04-2.85)	0.41
Lower respiratory inflammation	1.84 (1.40-2.43)	0.00	1.74 (1.27-2.39)	0.02[a]	1.77 (1.33-2.36)	0.00[a]	1.10 (0.61-1.98)	0.76	1.00 (0.51-1.93)	1.00	1.01 (0.55-1.85)	1.00	0.73 (0.36-1.49)	0.39	0.64 (0.28-1.47)	0.89	0.77 (0.38-1.58)	0.93	-	-	-	-	-	-
Diarrhea and vomiting (gastroenteritis)	0.86 (0.63-1.18)	0.35	0.79 (0.56-1.12)	0.89	0.80 (0.58-1.10)	0.75	1.22 (0.76-1.95)	0.40	0.91 (0.52-1.61)	1.00	1.14 (0.70-1.84)	1.00	1.05 (0.64-1.74)	0.84	1.03 (0.59-1.82)	1.00	1.10 (0.66-1.84)	1.00	1.53 (0.78-3.00)	0.21	0.88 (0.34-2.28)	1.00	1.41 (0.71-2.83)	1.00
Influenza	1.26 (0.90-1.77)	0.18	1.11 (0.75-	1.00	1.17 (0.83-1.66)	0.90	1.44 (0.82-2.55)	0.21	1.04 (0.52-2.08)	1.00	1.32 (0.74-2.36)	0.90	1.05 (0.55-1.99)	0.88	0.96 (0.47-1.98)	1.00	1.06 (0.56-2.03)	1.00	-	-	-	-	-	-
Exanthema subitum	1.00 (0.81-1.24)	0.97	1.03 (0.81-1.30)	1.00	1.00 (0.81-1.24)	1.00	1.08 (0.74-1.56)	0.70	0.97 (0.64-1.48)	1.00	1.04 (0.71-1.52)	1.00	1.08 (0.75-1.54)	0.68	1.26 (0.85-1.86)	0.89	1.18 (0.82-1.71)	0.90	1.55 (0.92-2.63)	0.10	1.69 (0.88-3.25)	0.71	1.99 (1.15-3.45)	0.25
Herpangina	1.18 (0.78-1.78)	0.44	1.12 (0.70-1.79)	1.00	1.18 (0.78-1.8)	0.93	1.58 (0.83-3.00)	0.16	2.01 (1.03-3.93)	0.71	1.63 (0.84-3.16)	0.75	0.58 (0.22-1.57)	0.28	0.70 (0.26-1.91)	1.00	0.59 (0.22-1.61)	0.90	-	-	-	-	-	-

Table IV. Continued.

	History of cervical cancer												History of other cancer											
	Transvaginal (n=609)						Caesarean (n=192)						Transvaginal (n=202)						Caesarean (n=80)					
Outcomes[b]	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value	Crude ORs (95% CI)	P-value	Adjusted ORs (95% CI)	q-value	Adjusted ORs using multiple imputation (95% CI)	q-value
Hand, foot and mouth disease	0.80 (0.55-1.15)	0.23	0.70 (0.45-1.08)	0.71	0.79 (0.54-1.16)	0.90	0.33 (0.12-0.90)	0.03	0.41 (0.15-1.11)	0.71	0.33 (0.12-0.9)	0.41	0.98 (0.55-1.76)	0.95	1.11 (0.59-2.07)	1.00	1.02 (0.56-1.86)	1.00	-	-	-	-	-	-
Adenovirus	1.06 (0.64-1.75)	0.82	1.25 (0.75-2.08)	0.92	1.01 (0.60-1.67)	1.00	0.77 (0.28-2.08)	0.60	0.56 (0.18-1.81)	0.92	0.64 (0.23-1.78)	1.00	0.20 (0.03-1.40)	0.10	0.25 (0.03-1.77)	0.89	0.21 (0.03-1.53)	0.75	-	-	-	-	-	-
Respiratory syncytial virus	0.84 (0.62-1.14)	0.27	0.75 (0.53-1.06)	0.71	0.79 (0.58-1.08)	0.75	1.40 (0.90-2.17)	0.14	1.31 (0.79-2.16)	0.89	1.37 (0.87-2.17)	0.75	0.92 (0.55-1.53)	0.74	1.05 (0.61-1.80)	1.00	0.97 (0.58-1.64)	1.00	1.00 (0.46-2.18)	0.99	1.47 (0.65-3.33)	0.92	1.06 (0.47-2.36)	1.00
Chickenpox	0.82 (0.50-1.35)	0.43	0.97 (0.58-1.61)	1.00	0.78 (0.47-1.30)	0.90	0.49 (0.16-1.53)	0.22	0.53 (0.17-1.69)	0.89	0.44 (0.14-1.39)	0.75	0.94 (0.41-2.11)	0.87	0.96 (0.39-2.37)	1.00	1 (0.44-2.27)	1.00	-	-	-	-	-	-

[a]Significance at q<0.05, adjusted using the Benjamin-Hochberg method for false detection rate; [b]Outcomes with an expected frequency of less than 5 were excluded from the analysis; [c]Covariates at 6 month of age: Maternal age at registration, maternal BMI before pregnancy, maternal smoking status, household income, pregnancy loss history, the presence/absence of IVF-ET, previous deliveries, sex of child, maternal allergy and ear, nose, and throat disease, congenital diseases of the child, feeding method at one month of age, number of family members currently living together with the child, the month of questionnaire entry at six months of age, the period of breast milk intake (until six month of age), the period of artificial nutrition intake (until six months of age), attendance at a childcare facility at six month of age (daycare center/nursery), influenza virus vaccination, rotavirus vaccination, and Haemophilus influenzae type b and pneumococcal vaccination; [d]Covariates at 1 year of age: we added the month of questionnaire entry at one year of age, the period of breast milk intake (until one year of age), the period of artificial nutrition intake (until one year of age), attendance at a childcare facility at one year of age (daycare center/nursery), employment status, influenza virus vaccination, rotavirus vaccination, Haemophilus influenzae type b and pneumococcal vaccination, palivizumab injection, and chickenpox vaccination to the covariates at six months of age.

surgery for Stage I cervical cancer is very low. He *et al* found that 78450 patients with a prior CIN 3 had an increase risk of preterm birth, chorioamnionitis, infant sepsis and neonatal death compared to 784500 matched controls (22). We should pay attention to chorioamnionitis, infant sepsis and neonatal death though we could not examine the risk. Persistent vaginal HPV-16/18 detection was reported to be significantly associated with preterm birth (23). The study to examine whether HPV vaccination has an effect to prevent it is also necessary.

In our present study, 56 women had cancer as a complication during pregnancy, however, details regarding treatment and age at cancer diagnosis were not available. This was one limitation of our study. The type of cancer was not taken into account in analysis since the number of women with a history of each specific cancer was small. The CIN 3 might be included in cervical cancer because questionnaires were self-administered. These were other limitations.

In conclusion, lower respiratory tract inflammation in one-year-old infants born by vaginal delivery increased significantly in cervical cancer survivors. No risk of other infant inflammations was found in the total group of survivors. Infants delivered from women with prior cervical cancer should be taken care till one year old. Further study concerning an association between HPV and lower respiratory inflammation is necessary. It was ascertained that preterm births increased in women with a history of cervical cancer, that caesarean section increased in all cancer survivors and that there was no increase in congenital anomalies in the cancer survivors as a whole. It is important to provide this information to cancer survivors before they become pregnant.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) but are available from the corresponding author on reasonable request. Ethical Guidelines for Epidemiological Research enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

Authors' contributions

The JECS group conducted the nationwide study project. RN wrote the first draft of the manuscript. MSO designed the present study and analyzed the data. TM and HT analyzed the data. TE organized the study team, and was responsible for obtaining and analyzing the data. MK was responsible for data acquisition and supervision of the study. RN, SK, KK and SS were responsible for data acquisition. MK and TE confirm the authenticity of all the raw data. All authors interpreted the data, contributed to the writing of the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The JECS was approved by the Institutional Review Board of the Japan National Institute for Environmental Studies (approval no. 100910001), as well as by the ethics committees of all participating institutions. This study was conducted with the approval of the Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences (approval nos. 554 and 554-2). Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Anderson C, Engel SM, Mersereau JE, Black KZ, Wood WA, Anders CK and Nichols HB: Birth outcomes among adolescent and young adult cancer survivors. JAMA Oncol 3: 1078-1084, 2017.
2. Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, Ginsberg JP, Kenney LB, Levine JM, Robison LL, *et al*: Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: A report from the childhood cancer survivor study cohort. Lancet Oncol 17: 567-576, 2016.
3. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW and Wallace WHB: The impact of cancer on subsequent chance of pregnancy: A population-based analysis. Hum Reprod 33: 1281-1290, 2018.

4. Velez MP, Richardson H, Baxter NN, McClintock C, Greenblatt E, Barr R and Green M: Risk of infertility in female adolescents and young adults with cancer: A population-based cohort study. Hum Reprod 36: 1981-1988, 2021.
5. Haggar FA, Pereira G, Preen D, Holman CD and Einarsdottir K: Adverse obstetric and perinatal outcomes following treatment of adolescent and young adult cancer: A population-based cohort study. PLoS One 9: e113292, 2014.
6. Armuand G, Svanberg AS, Bladh M and Sydsjö G: Adverse obstetric outcomes among female childhood and adolescent cancer survivors in Sweden: A population-based matched cohort study. Acta Obstet Gynecol Scand 98: 1603-1611, 2019.
7. Japan Society of Obstetrics and Gynecology. Cervical Cancer. https://www.jsog.or.jp/modules/diseases/index.php?content_id=10
8. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, Yamagata Z, Kayama F, Kishi R, Ohya Y, *et al*: Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health 14: 25, 2014.
9. Suzuki K, Shinohara R, Sato M, Otawa S and Yamagata Z: Association between maternal smoking during pregnancy and birth weight: An appropriately adjusted model from the Japan environment and children's study. J Epidemiol 26: 371-377, 2016.
10. Ishitsuka K, Nakayama SF, Kishi R, Mori C, Yamagata Z, Ohya Y, Kawamoto T and Kamijima M: Japan environment and children's study: Backgrounds, activities, and future directions in global perspectives. Environ Health Prev Med 22: 61, 2017.
11. Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, Suda E, Ono M, Yonemoto J, Iwai-Shimada M, *et al*: Japan environment and children's study group. Baseline profile of participants in the Japan environment and children's study (JECS). J Epidemiol 28: 99-104, 2018.
12. Sugiura-Ogasawara M, Ebara T, Matsuki T, Yamada Y, Omori T, Matsumoto Y, Kato S, Kano H, Kurihara T, Saitoh S, *et al*: Endometriosis and recurrent pregnancy loss as new risk factors for venous thromboembolism during pregnancy and post-partum: The JECS birth cohort. Thromb Haemost 119: 606-617, 2019.
13. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ and Egger M: Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. PLoS Med 4: e297, 2007.
14. Moreno I and Simon C: Relevance of assessing the uterine microbiota in infertility. Fertil Steril 110: 337-343, 2018.
15. Shao Y, Forster SC, Tsaliki E, Vervier K, Strang A, Simpson N, Kumar N, Stares MD, Rodger A, Brocklehurst P, *et al*: Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. Nature 574: 117-121, 2019.
16. Słabuszewska-Jóźwiak A, Szymański JK, Ciebiera M, Sarecka-Hujar B and Jakiel G: Pediatrics consequences of caesarean section-a systematic review and meta-analysis. Int J Environ Res Public Health 17: 8031, 2020.
17. Alterman N, Kurinczuk JJ and Quigley MA: Caesarean section and severe upper and lower respiratory tract infections during infancy: Evidence from two UK cohorts. PLoS One 16: e0246832, 2021.
18. Chorna N, Romaguera J and Godoy-Vitorino F: Cervicovaginal microbiome and urine metabolome paired analysis reveals niche partitioning of the microbiota in patients with human papilloma virus infections. Metabolites 10: 36, 2020.
19. Sims TT, El Alam MB, Karpinets TV, Dorta-Estremera S, Hegde VL, Nookala S, Yoshida-Court K, Wu X, Biegert GWG, Medrano AY, *et al*: Gut microbiome diversity is an independent predictor of survival in cervical cancer patients receiving chemoradiation. Commun Biol 4: 237, 2021.
20. Ji J, Sundquist J and Sundquist K: Stillbirth and neonatal death among female cancer survivors: A national cohort study. Int J Cancer 139: 1046-1052, 2016.
21. Nitecki R, Floyd J, Lamiman K, Clapp MA, Fu S, Jorgensen K, Melamed A, Brady PC, Kaimal A, Del Carmen MG, *et al*: Outcomes of the first pregnancy after fertility-sparing surgery for early-stage cervical cancer. Obstet Gynecol 138: 565-573, 2021.
22. He W, Sparén P, Fang F, Sengpiel V, Strander B and Czene K: Pregnancy outcomes in women with a prior cervical intraepithelial neoplasia grade 3 diagnosis: A nationwide population-based cohort study with sibling comparison design. Ann Intern Med 175: 210-218, 2022.
23. Niyibizi J, Mayrand MH, Audibert F, Monnier P, Brassard P, Laporte L, Lacaille J, Zahreddine M, Bédard MJ, Girard I, *et al*: Association between human papillomavirus infection among pregnant women and preterm birth. JAMA Netw Open 4: e2125308, 2021.