Adverse Birth and Obstetric Outcomes in the Offspring of Male Adolescent and Young Adult Cancer Survivors: A Nationwide Population-Based Study

Wei-Heng Kao[1,2,3], Yi-Fang Chuang[2,4,5], Yi-Wei Huang[6], Po-Jui Chen[1], Yu-Cheng Liu[7], Chun-Chieh Wang[1,8], Jun-Te Hsu[9], Pei-Wei Shueng[10,11], and Chang-Fu Kuo[3,12,13]

ABSTRACT

Background: The growing population of male adolescent and young adult (AYA, ages 15–40 years) cancer survivors has heightened interest in their reproductive health. However, studies have reported conflicting findings on the potential risks of cancer and its treatments on birth and obstetric outcomes.

Methods: We used encrypted identification numbers for both fathers and mothers to link three nationwide Taiwan datasets from 2004 to 2019, identifying 3,785 births with a paternal history of AYA cancer. For comparison, we included 37,850 matched fathers without a cancer history, matched by paternal age and infant birth year. We used multivariable logistic regression analysis to identify independent associations between adverse birth outcomes (e.g., preterm labor, low birthweight, and congenital malformations) and obstetric outcomes (e.g., fetal growth restriction, threatened labor, and threatened abortion) and being born to male AYA cancer survivors.

Results: The offspring of male AYA cancer survivors did not exhibit a significantly increased risk of adverse birth (OR = 1.0; 95% confidence interval, 0.9−1.1) or obstetric (OR = 1.1; 95% confidence interval, 1.0−1.1) outcomes compared with offspring born to cancer-free matched fathers. Furthermore, the risk of preterm labor, low birthweight, congenital malformations, fetal growth restriction, and threatened labor or miscarriage was comparable between groups.

Conclusions: Paternal cancer history during adolescence or young adulthood does not seem to increase the risk of adverse birth or obstetric outcomes in offspring.

Impact: This study reassures the reproductive health of this population, providing valuable insights for oncology and reproductive medicine, potentially influencing patient counseling and guidelines.

Introduction

The NCI defines adolescents and young adults (AYA), ages 15 to 39 years, as a distinct group in cancer care and research due to unique characteristics in this population compared with other age groups (1). These include differences in the prevalence of specific cancer types, prognosis, and survivorship outcomes (2). Unfortunately, cancer rates in AYAs have been gradually increasing over the past two decades in both Eastern and Western countries (2–4). For example, in Taiwan, the incidence of cancer in individuals ages 15 to 39 years increased from 56.1 to 72.1 new cases per 100,000 people between 2000 and 2020 (5). In addition, the concurrent advances in cancer therapeutics and medical care have led to improved survival rates (2), resulting in a growing number of AYA cancer survivors.

It is increasingly recognized that anticancer therapies, including chemotherapy (CT) and radiotherapy (RT), can impair fertility and reproductive function (6). Such treatments can also induce DNA damage in gametes, which may result in genetic abnormalities in the offspring (7). Consequently, a paternal history of cancer during adolescence or young adulthood may be linked to genetic abnormalities, which could potentially result in fetal developmental anomalies and adverse birth outcomes. However, published studies have reported mixed findings. A research study integrating data from Danish and Swedish registries found a higher prevalence of major congenital anomalies in infants born to male cancer survivors across all ages, although no significant association was observed with low birthweight or preterm labor (8). A separate Norwegian study reported an increased risk of congenital anomalies in the offspring of male survivors diagnosed between 15 and 35 years of age (9). Conversely, another analysis from the same registry did not confirm this relationship for survivors diagnosed between 16 and 45 years of age (10).

In general, research on adverse birth and obstetric outcomes in the offspring of male AYA cancer survivors remains limited compared with studies focusing on female AYA cancer survivors (11–15). Given the inconsistencies in the literature and the lack of

[1]Department of Radiation Oncology, Chang Gung Memorial Hospital, Taoyuan, Taiwan. [2]Institute of Public Health, National Yang Ming Chiao Tung University, Taipei, Taiwan. [3]School of Medicine, National Tsing Hua University, Taipei, Taiwan. [4]Department of Psychiatry, Far Eastern Memorial Hospital, Taipei, Taiwan. [5]International Health Program, National Yang Ming Chiao Tung University, Taipei, Taiwan. [6]Center for Artificial Intelligence in Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan. [7]Department of Gynecology and Obstetrics, Chang Gung Memorial Hospital, Taipei, Taiwan. [8]Department of Medical Imaging and Radiological Science, Chang Gung University, Taoyuan, Taiwan. [9]Department of General Surgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan. [10]Division of Radiation Oncology, Department of Radiology, Far Eastern Memorial Hospital, New Taipei City, Taiwan. [11]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan. [12]Division of Rheumatology, Allergy, and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan. [13]Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, United Kingdom.

P.-W. Shueng and C.-F. Kuo contributed equally to this article.

Corresponding Author: Chang-Fu Kuo, Division of Rheumatology, Allergy, and Immunology, Chang Gung Memorial Hospital, No. 5, Fuxing Street, Taoyuan 333, Taiwan. E-mail: zandis@gmail.com

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data from Eastern countries, we conducted a retrospective, nationwide, population-based cohort study in Taiwan. This study aims to investigate whether a paternal history of cancer during adolescence or young adulthood is associated with adverse birth and obstetric outcomes in the offspring.

Materials and Methods

Study design and data sources

This nationwide, retrospective, population-based cohort study integrated data from three major Taiwanese databases: the Taiwan Maternal and Child Health (TMCH) database, the Taiwan National Health Insurance (NHI) dataset, and the Taiwan Birth Reporting System (TBRS). We initially identified the fathers, mothers, and infants in the TMCH database and linked the fathers to the NHI dataset using unique identification numbers to confirm the diagnosis of AYA cancer. Subsequently, we connected these mothers to the TBRS and NHI databases to extract data on adverse outcomes.

The TMCH database combines information from several national registries, enabling unique identification of mothers, fathers, and their offspring through cross-validation of data (16). The NHI database (RRID: SCR_026048), launched in 1996, includes more than 99.5% of the Taiwanese population. This extensive dataset contains information on health services like prescriptions, outpatient visits, and hospital stays. The maternal care records included in the NHI dataset provide specifics on fetal ultrasounds, deliveries, and postpartum care for mothers and infants. Cancer and comorbidity diagnoses were coded using the International Classification of Diseases (ICD), Ninth Revision codes until January 2016, when the NHI database transitioned to the ICD, Tenth Revision codes. A comprehensive list of the disease codes used in this study is provided in Supplementary Table S1. The following data were extracted from the dataset: cancer diagnoses and treatments, demographic and socioeconomic characteristics for both parents, medication use, paternal comorbidities, paternal lifestyle factors, and adverse obstetric outcomes. The TBRS (RRID: SCR_026047) was established in 1993 under Taiwan's Child Welfare Act. Under this law, all medical institutions are legally obligated to submit birth certifications for live births and stillbirths meeting specific criteria to the health authority. The birth certifications cover infants with birthweights exceeding 500 g or gestational ages of 20 weeks or longer. The TBRS subsequently rectifies potential errors and validates the provided information. Significant enhancements in the accuracy of TBRS data have been realized following the transition from a paper-based system to a fully electronic online platform in 2004. Consequently, this study selected data beginning from that year. For the current research, data extracted from the TBRS included information on adverse birth outcomes and delivery methods.

Study participants

The Chung Gung Medical Foundation Institutional Review Board, which reviews in accordance with the Declaration of Helsinki, approved the study (reference: 202201960B1) and waived the requirement for written informed consent. The TMCH database was initially utilized to obtain unique identification numbers for fathers, mothers, and their offspring. Linkages were then established to the NHI and TBRS datasets to extract the 2004 to 2019 data for the identified subjects. For this study, we focused specifically on fathers of firstborn singleton children, using NHI data to scrutinize whether they had received a cancer diagnosis between 15 and 39 years of age. We excluded fathers who were diagnosed with cancer either before 15 years or after 39 years of age prior to the date of pregnancy. Similarly, fathers who had been treated with CT or RT before the age of 15 years were not eligible. Cancer treatments were classified as CT according to medication codes or as RT based on procedural codes (13). Due to the complexity of comprehensively defining surgical procedure codes for oncologic treatments, we categorized treatment groups into the following: CT alone, RT alone, CT combined with RT, and a group receiving neither CT nor RT. Survivors in the group receiving neither CT nor RT likely underwent primarily surgical interventions as their main modality of cancer treatment. We excluded mothers from the study if they met any of the following criteria: (i) received a cancer diagnosis prior to delivery, (ii) were younger than 15 years or older than 49 years of age at the time of delivery, or (iii) had an interpregnancy interval of <3 months or >20 years. The third criterion was implemented to eliminate potentially erroneous records from the datasets. Due to the TMCH database's exclusive focus on live births, cases involving fathers with a history of AYA cancer and their stillborn infants were exceedingly rare. Consequently, these uncommon cases were excluded from the analysis to maintain the study's focus on live birth outcomes. After applying these criteria, we identified a total of 3,785 live births to male AYA cancer survivors. For AYA fathers without a prior cancer diagnosis, we used the nearest neighbor matching method to match the father's age and the year of the infant's birth with a 1:10 ratio. A final comparison group of 37,850 male AYAs was identified (**Fig. 1**).

Adverse outcomes

Adverse outcomes were categorized into two main groups: adverse birth outcomes and adverse obstetric outcomes. Adverse birth outcomes data were obtained from the TBRS database and included low birthweight (<2,500 g), preterm labor (before 37 weeks of gestation), small for gestational age (birthweight less than the 10th percentile for gestational age), large for gestational age (birthweight greater than the 90th percentile for gestational age), a 5-minute Apgar score <7, congenital malformations, and fetal distress (13). The criteria used to classify infants as small or large for gestational age were based on a nomogram developed using data on all live births recorded in the TBRS database from 2004 to 2019. Malformation information was abstracted from among preidentified conditions within the TBRS database, which uses a comprehensive classification system categorizing malformations across physiologic systems including, but not limited to, the nervous, cardiovascular, digestive, and urinary systems. The adverse obstetric outcomes included antepartum/postpartum hemorrhage, premature rupture of membranes, induction of labor, threatened abortion or threatened labor requiring hospitalization, and fetal growth restriction (12). Because the available data did not distinguish between elective and emergent Cesarean sections, both were combined into a single Cesarean delivery outcome rather than being classified separately. The ICD codes used to identify the study outcomes are listed in Supplementary Table S1.

Covariates

We obtained demographic and socioeconomic data from the NHI database, including the child's date of birth along with the mother's age, father's age, father's place of residence, income level, and occupation. The methodology for coding residence location, income level, and occupation categories has been previously described (12, 13). The paternal comorbid conditions examined in the study included cardiovascular, autoimmune, liver, renal, pulmonary, and hematologic

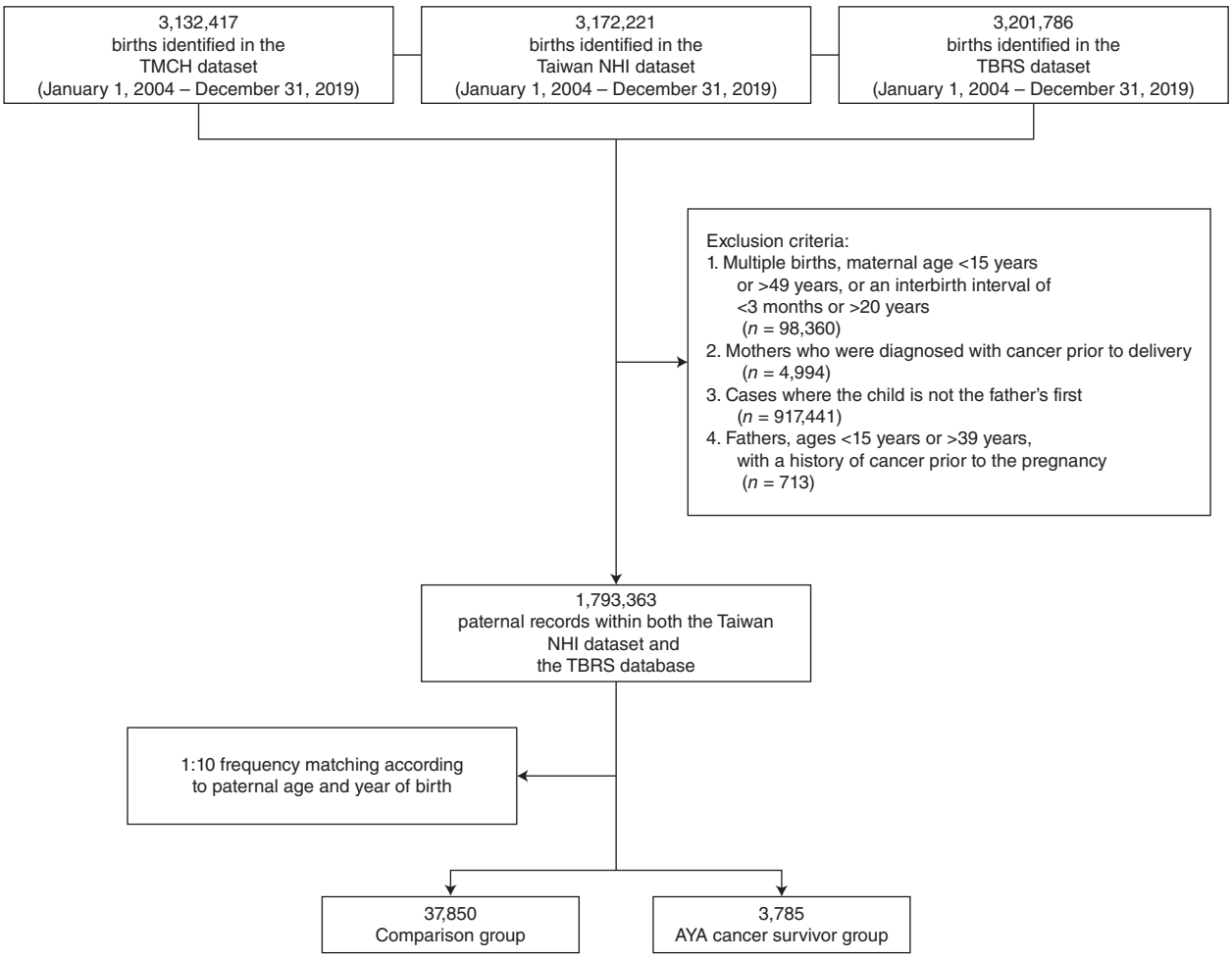

Figure 1.

Flow chart of study participant selection. This flow chart illustrates the selection process for study participants. Male AYA cancer survivors were identified from the Taiwan NHI dataset. After applying inclusion and exclusion criteria and a 1:10 matching ratio, 3,785 male AYA cancer survivors were matched with 37,850 individuals in the comparison group.

diseases, hypertension, and diabetes mellitus. For fathers with a history of cancer during adolescence or young adulthood, comorbidities were collected prior to their tumor diagnosis date (i.e., index date). For fathers in the comparison group, comorbidities were gathered on the index date corresponding to the matched AYA cancer survivor. A father was classified as having a comorbid condition if the relevant ICD code occurred at least twice in outpatient records or once in inpatient records. This algorithm for defining comorbidities using NHI data has been validated in multiple prior studies (17–19). Similarly, the definition of lifestyle factors, such as smoking and alcohol misuse before pregnancy, was based on the presence of specific ICD codes in the NHI database. Based on findings from previous work (20), medications categorized in the Anatomical Therapeutic Chemical Classification system under codes C (cardiovascular system), J (anti-infectives for systemic use), and N (nervous system) were classified as "high-risk" drugs, along with other specific molecules (e.g., allopurinol and omeprazole). Fathers prescribed any of these drugs in the 90 days before their partner's last menstrual period through the date of the last menstrual period were defined as high-risk medication users.

Statistical analysis

Logistic regression analysis was conducted to calculate ORs and their corresponding 95% confidence intervals (CI), quantifying the risk of each adverse outcome among offspring of male AYA cancer survivors relative to the comparison group. The final multivariable model was adjusted for a comprehensive set of potential confounding factors, encompassing infant characteristics such as birth year and sex; parental characteristics including maternal age, paternal age, paternal comorbidities, lifestyle factors (smoking or alcohol misuse before pregnancy), and usage of high-risk medications; and sociodemographic factors comprising nationality, residential location, income level, and occupation. To ensure the robustness and validity of the findings, several sensitivity analyses were conducted. We initially examined the risks of all adverse outcomes across an expanded cancer diagnosis age range (15–49 years).

The associations were further examined considering different intervals between cancer diagnosis and delivery (<2 years vs. ≥2 years) and different ages at diagnosis. Finally, focused analyses were carried out considering the five most prevalent malignancies in Taiwanese men (head and neck cancer, gastrointestinal cancer, endocrine cancer, male genital cancer, and lymphoma). All analyses were conducted using SAS software, version 9.4 (SAS Institute, RRID: SCR_008567). Two-tailed P values < 0.05 were considered statistically significant.

Data availability

This study used data from the TMCH database, Taiwan NHI database, and TBRS, provided by the Taiwan Health and Welfare Data Science Center. Access to the data was obtained through an approved data usage license application submitted per the center's guidelines. The fully anonymized data are available for research purposes with permission from the Taiwan Health and Welfare Data Science Center at https://dep.mohw.gov.tw/DOS/cp-5119-59201-113.html.

Results

General characteristics of the study participants

Table 1 presents the general characteristics of fathers with and without a history of cancer during adolescence or young adulthood. Because of matching, the median paternal age in both groups was 35.4 years. Additionally, the median maternal age in the offspring born to male AYA cancer survivors was similar to that observed in the comparison group. A higher incidence of comorbidities was noted within the AYA cancer survivor group. The distribution of birth years for infants born to male AYA cancer survivors was as follows: 857 infants were born between 2004 and 2007; 812 infants between 2008 and 2011; 1,025 infants between 2012 and 2015; and 1,088 infants between 2016 and 2019. The most common cancer types were head and neck cancer (22.0%), gastrointestinal cancer (15.9%), endocrine cancer (12.5%), male genital cancer (10.9%), and lymphoma (10.4%). Within head and neck cancers, nasopharyngeal carcinoma was the most prevalent subtype (47.1% of head and neck cancers). For gastrointestinal cancers, the most common subtypes were liver and biliary (35.0%) and colon cancers (31.3%). Thyroid cancer accounted for the majority (98.1%) of endocrine cancers, whereas testicular malignancies represented 95.9% of male genital cancers. Finally, among lymphomas, the ratio of Hodgkin lymphoma to non–Hodgkin lymphoma was approximately 3:7.

Risk of adverse outcomes

The ORs for overall adverse birth outcomes (OR = 1.0; 95% CI, 0.9–1.1) and overall adverse obstetric outcomes (OR = 1.1; 95% CI, 1.0–1.1) showed no statistically significant increase in the offspring of fathers with a history of cancer during adolescence or young adulthood relative to the comparison group (**Table 2**). Specifically, we found no evidence of a higher risk of congenital malformations (OR = 1.0; 95% CI, 0.8–1.1), preterm labor (OR = 1.0; 95% CI, 0.9–1.2), or low birthweight (OR = 1.1; 95% CI, 1.0–1.3). Furthermore, Cesarean delivery rates were similar between the two groups (36.2% vs. 35.7%; OR = 1.0; 95% CI, 0.9–1.0).

Impact of cancer treatments

Among male AYA cancer survivors, 2,156 (57%) did not receive CT or RT. Of the survivors who had undergone treatment, 733 (19.4%) received CT alone, 294 (7.8%) received RT alone, and 602 (15.9%) received both CT and RT (**Table 3**). When comparing the risk of overall adverse birth and obstetric outcomes across these four treatment groups with that of male AYAs without a cancer diagnosis, no significant differences were observed (adverse birth outcomes: OR = 0.9; 95% CI, 0.8–1.1; adverse obstetric outcomes: OR = 1.0; 95% CI, 0.8–1.2; **Table 3**). Moreover, within each of the four treatment groups, there was no significantly increased risk for specific adverse outcomes, including congenital malformations, preterm labor, and low birthweight, when compared with male AYAs without a cancer diagnosis. Furthermore, no significant differences were observed in the rates of Cesarean delivery across all treatment groups.

Sensitivity analyses

Sensitivity analyses, which included 4,222 survivors diagnosed between 15 and 49 years of age, revealed no increased risks for overall adverse birth outcomes, obstetric complications, or congenital malformations (Supplementary Table S2). Analyses of the five most common cancer types also showed no significant increases in overall adverse birth and obstetric outcomes (Supplementary Table S3). However, the offspring of paternal lymphoma survivors had a higher risk of showing 5-minute Apgar scores <7 (OR = 2.7; 95% CI, 1.1–6.8), whereas the offspring of genital cancer survivors had an increased risk of labor induction (OR = 2.2; 95% CI, 1.3–3.7). The odds of congenital malformations were not significantly increased for any of the five major cancer types, including male genital cancer. In addition, no significant increases in the risk of adverse outcomes were observed in the analyses categorized by age at diagnosis (15–29 years vs. 30–39 years; Supplementary Table S4) or time from diagnosis to the first child (<2 years vs. ≥2 years; Supplementary Table S5) relative to comparison subjects. An increased risk of presenting with a 5-minute Apgar score <7 (OR = 1.9; 95% CI, 1.1–3.2) was observed among children whose fathers were diagnosed with cancer between 15 and 29 years of age. No other increased risks were identified. When analyses were categorized by time since diagnosis, increased risks were noted only for fetal growth restriction (OR = 1.6, 95% CI, 1.1–2.3) and pregnancies requiring labor induction (OR = 1.8, 95% CI, 1.1–2.9) in the group with <2 years between diagnosis and childbirth.

Discussion

In this retrospective population-based cohort study of nearly 40,000 Taiwanese fathers and their first singleton children, we examined whether a paternal history of cancer during adolescence or young adulthood could be associated with an increased risk of adverse birth and obstetric outcomes in the offspring. Our findings did not support a relationship between being born to a male AYA cancer survivor and an increased risk of adverse outcomes compared with male AYAs without a previous cancer diagnosis. Further analyses in relation to treatment modalities and cancer types did not identify any specific risk subgroups.

In keeping with our findings, Stensheim and colleagues (10) found no significant increase in congenital anomalies among children born to Norwegian male AYA cancer survivors ages 16 to 45 years. Al-Jebari and colleagues (21) also reported no significantly increased risk using data from the Swedish database for all paternal cancer diagnoses. However, studies using Scandinavian registries present conflicting results. Magelssen and colleagues (9) identified a 1.5-fold increased risk for children of male AYA cancer survivors

Table 1. General characteristics of fathers with and without a positive history of cancer during adolescence or young adulthood.

Variable	Negative cancer history, *n* = 37,850 *n* (%)	Positive cancer history, *n* = 3,785 *n* (%)
Maternal age at delivery		
15–24 years	2,780 (7.3)	297 (7.9)
25–34 years	25,418 (67.2)	2,528 (66.8)
≥35 years (maximum: 48 years)	9,652 (25.5)	960 (25.4)
Median (first quartile–third quartile), years	31.8 (28.6–35.0)	31.8 (28.6–35.0)
Paternal age at delivery		
15–24 years	347 (0.9)	35 (0.9)
25–34 years	16,814 (44.4)	1,684 (44.5)
35–44 years	19,416 (51.3)	1,939 (51.2)
≥45 years (maximum: 56 years)	1,273 (3.4)	127 (3.4)
Median (first quartile–third quartile), years	35.4 (32.4–38.8)	35.4 (32.4–38.8)
Infant sex		
Male	19,738 (52.2)	1,975 (52.2)
Female	18,112 (47.9)	1,810 (47.8)
Infant birth year		
2004–2007	8,570 (22.6)	857 (22.6)
2008–2011	8,150 (21.5)	815 (21.5)
2012–2015	10,250 (27.1)	1,025 (27.1)
2016–2019	10,880 (28.8)	1,088 (28.8)
Paternal comorbidities		
Hypertension	79 (0.2)	151 (4.0)
Cardiovascular disease	103 (0.3)	49 (1.3)
Autoimmune disease	175 (0.5)	25 (0.7)
Liver disease	489 (1.3)	178 (4.7)
Diabetes mellitus	21 (0.1)	16 (0.4)
Renal disease	49 (0.1)	19 (0.5)
Pulmonary disease	246 (0.7)	25 (0.7)
Hematologic disease	64 (0.2)	42 (1.1)
Paternal lifestyle risk factors		
Smoking before pregnancy	1,250 (3.3)	124 (3.3)
Alcohol misuse before pregnancy	54 (0.1)	11 (0.3)
High-risk medication use	9,841 (26.0)	1,475 (39.0)
Paternal cancer types		
Head and neck cancer		833 (22.0)
Gastrointestinal cancer		600 (15.9)
Endocrine system cancer		473 (12.5)
Male genital cancer		414 (10.9)
Lymphoma		395 (10.4)
Others		1,070 (28.2)
Paternal cancer treatments		
CT alone		733 (19.4)
CT plus RT		602 (15.9)
Neither CT nor RT		2,156 (57.0)
RT alone		294 (7.8)
Paternal nationality		
Taiwanese	37,743 (99.7)	3,776 (99.8)
Paternal place of residence		
Urban	21,043 (55.6)	2,074 (54.8)
Suburban	13,469 (35.6)	1,344 (35.5)
Rural	3,338 (8.8)	367 (9.7)
Paternal income levels (New Taiwan dollars)		
Quintile 1 (20,100)	6,486 (17.1)	619 (16.4)
Quintile 2 (26,400)	6,499 (17.3)	662 (17.5)
Quintile 3 (40,100)	7,706 (20.4)	793 (21.0)
Quintile 4 (55,400)	7,667 (20.3)	769 (20.3)
Quintile 5 (182,000)	9,492 (25.1)	942 (24.9)
Paternal occupation		
Dependents of insured individuals	1,383 (3.7)	155 (4.1)

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Table 1. General characteristics of fathers with and without a positive history of cancer during adolescence or young adulthood. (Cont'd)

Variable	Negative cancer history, *n* = 37,850 *n* (%)	Positive cancer history, *n* = 3,785 *n* (%)
Civil servants, teachers, military personnel, and veterans	2,501 (6.6)	273 (7.2)
Nonmanual workers and professionals	23,399 (61.8)	2,295 (60.6)
Manual workers/others	10,567 (27.9)	1,062 (28.1)

diagnosed at ages 15 to 35 years in Norway, whereas Ståhl and colleagues (8) observed a 1.17-fold increased risk in combined data from Denmark and Sweden across all age groups.

The distribution of male AYA cancer types varies between Eastern and Western countries (2–4). In Western countries, testicular cancer is the most common cancer type among male AYAs (2, 4), whereas it ranks as only the fifth most common cancer type in Taiwan (5). Consequently, testicular cancer survivors constituted approximately 10% of our study population, which is notably lower than the 28% to 50% reported in previous studies (8–10). This discrepancy in cancer-type distribution may contribute to the differences observed between our results and those of prior investigations. However, our analysis of 414 male genital cancer survivors did not reveal a significant increase in congenital malformations, although the number of survivors and events was limited, warranting cautious interpretation.

Cancer and its treatments can disrupt normal spermatogenesis through multiple mechanisms. One of the most relevant is the overproduction of reactive oxygen species, leading to oxidative stress and damage to sperm DNA (22). Additionally, both CT and RT are genotoxic and can cause a range of genetic alterations in spermatozoa, from single-gene mutations to chromosomal abnormalities. This genetic damage may in turn lead to abnormal phenotypes in the offspring born to fathers with a history of cancer (23). However, contrary to this hypothesis, we found a comparable rate of congenital malformations (approximately 4.9%) in children born to male AYA cancer survivors and AYAs without a history of cancer. Furthermore, detailed analyses categorized by treatment type, cancer diagnosis, age at diagnosis, and time between diagnosis and birth failed to identify specific subgroups with an increased risk of congenital anomalies. One plausible explanation for the observed results is that malignancies and anticancer treatments predominantly cause disrupted fertility in male patients. This is supported by the high 15% to 30% infertility rate observed in male cancer survivors (24). Additionally, most fetuses with chromosomal abnormalities are likely to miscarry. However, as the study only examined live births, the risks associated with miscarriages or fetal deaths may have been underestimated. Consequently, the outcomes of our study should be interpreted within the context of live births, indicating that if a male AYA survivor fathers a child who is born alive, the risk of adverse outcomes is rare.

This research has several notable strengths. First, we implemented a comprehensive assessment of risk factors for adverse birth and obstetric outcomes, accounting for paternal health conditions, lifestyle factors,

Table 2. Outcomes observed in the offspring born to fathers with and without a positive history of cancer during adolescence or young adulthood.

Outcome	Comparison group, *n* = 37,850 *n* (%)	Positive cancer history, *n* = 3,785 *n* (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Overall adverse birth outcomes	11,938 (31.5)	1,184 (31.3)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Large for gestational age	3,570 (9.4)	386 (10.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Small for gestational age	3,807 (10.1)	367 (9.7)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Preterm labor	2,712 (7.2)	280 (7.4)	1.0 (0.9–1.2)	1.0 (0.9–1.2)
Low birthweight	2,657 (7.0)	293 (7.7)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
5-minute Apgar score <7	173 (0.5)	23 (0.6)	1.3 (0.9–2.1)	1.3 (0.8–2.0)
Congenital malformation	1,890 (5.0)	185 (4.9)	1.0 (0.8–1.1)	1.0 (0.8–1.1)
Fetal distress	1,405 (3.7)	129 (3.4)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
Overall adverse obstetric outcomes	9,581 (25.3)	1,007 (26.6)	1.1 (1.0–1.2)	1.1 (1.0–1.1)
Antepartum hemorrhage	3,343 (8.8)	331 (8.8)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Postpartum hemorrhage	477 (1.3)	46 (1.2)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Fetal growth restriction	1,514 (4.0)	167 (4.4)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Threatened labor or threatened abortion	2,694 (7.1)	289 (7.6)	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Premature rupture of membranes	3,037 (8.0)	305 (8.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Induction of labor	714 (1.9)	84 (2.2)	1.2 (0.9–1.5)	1.1 (0.9–1.4)
Cesarean delivery	13,717 (36.2)	1,350 (35.7)	1.0 (0.9–1.0)	1.0 (0.9–1.0)

[a]Adjusted for maternal age at delivery, paternal age at delivery, infant sex, infant birth year, hypertension, cardiovascular disease, autoimmune disease, liver disease, diabetes mellitus, renal disease, pulmonary disease, hematologic disease, smoking before pregnancy, alcohol misuse before pregnancy, use of high-risk drugs before pregnancy, paternal nationality, paternal place of residence, paternal income levels (New Taiwan dollars), and paternal occupation.

Table 3. Outcomes observed in the offspring born to fathers with and without a positive history of cancer during adolescence or young adulthood, with the former group categorized according to the treatment.

		Positive cancer history							
	Comparison group, *n* = 37,850	Neither CT nor RT, *n* = 2,156		CT alone, *n* = 733		RT alone, *n* = 294		CT with RT, *n* = 602	
Outcome	*n* (%)	*n* (%)	Adjusted OR[a] (95% CI)	*n* (%)	Adjusted OR[a] (95% CI)	*n* (%)	Adjusted OR[a] (95% CI)	*n* (%)	Adjusted OR[a] (95% CI)
Overall adverse birth outcome	11,938 (31.5)	678 (31.4)	1.0 (0.9–1.1)	240 (32.7)	1.1 (0.9–1.2)	84 (28.6)	0.9 (0.7–1.1)	182 (30.2)	0.9 (0.8–1.1)
Large for gestational age	3,570 (9.4)	222 (10.3)	1.1 (0.9–1.3)	73 (10.0)	1.1 (0.8–1.4)	34 (11.6)	1.3 (0.9–1.9)	57 (9.5)	1.0 (0.8–1.3)
Small for gestational age	3,807 (10.1)	214 (9.9)	1.0 (0.9–1.2)	75 (10.2)	1.0 (0.8–1.3)	22 (7.5)	0.7 (0.5–1.1)	56 (9.3)	0.9 (0.7–1.2)
Preterm labor	2,712 (7.2)	155 (7.2)	1.0 (0.8–1.2)	57 (7.8)	1.1 (0.8–1.4)	22 (7.5)	1.1 (0.7–1.7)	46 (7.6)	1.1 (0.8–1.4)
Low birthweight	2,657 (7.0)	170 (7.9)	1.2 (1.0–1.4)	58 (7.9)	1.1 (0.9–1.5)	17 (5.8)	0.8 (0.5–1.3)	48 (8.0)	1.1 (0.8–1.5)
5-minute Apgar score <7	173 (0.5)	14 (0.7)	1.4 (0.8–2.5)	≤8[b]	1.2 (0.4–3.2)	≤8[b]	1.5 (0.4–6.3)	≤8[b]	1.0 (0.3–3.1)
Congenital malformation	1,890 (5.0)	109 (5.1)	1.0 (0.8–1.2)	39 (5.3)	1.1 (0.8–1.6)	11 (3.7)	0.6 (0.3–1.2)	26 (4.3)	0.9 (0.6–1.3)
Fetal distress	1,405 (3.7)	73 (3.4)	0.9 (0.7–1.2)	25 (3.4)	0.9 (0.6–1.4)	≤8[b]	0.6 (0.3–1.4)	24 (4.0)	1.0 (0.7–1.6)
Overall adverse obstetric outcomes	9,581 (25.3)	592 (27.5)	1.1 (1.0–1.2)	185 (25.2)	1.0 (0.8–1.2)	82 (27.9)	1.1 (0.9–1.4)	148 (24.6)	1.0 (0.8–1.2)
Antepartum hemorrhage	3,343 (8.8)	185 (8.6)	1.0 (0.8–1.1)	62 (8.5)	1.0 (0.7–1.3)	29 (9.9)	1.1 (0.7–1.6)	55 (9.1)	1.0 (0.8–1.4)
Postpartum hemorrhage	477 (1.3)	28 (1.3)	1.1 (0.7–1.6)	≤8[b]	0.7 (0.3–1.6)	≤8[b]	0.3 (0.0–2.1)	10 (1.7)	1.2 (0.7–2.3)
Fetal growth restriction	1,514 (4.0)	89 (4.1)	1.0 (0.8–1.3)	35 (4.8)	1.2 (0.9–1.7)	17 (5.8)	1.5 (0.9–2.4)	26 (4.3)	1.1 (0.7–1.6)
Threatened labor or threatened abortion	2,694 (7.1)	168 (7.8)	1.1 (0.9–1.3)	53 (7.2)	1.0 (0.8–1.4)	23 (7.8)	1.1 (0.7–1.7)	45 (7.5)	1.1 (0.8–1.4)
Premature rupture of membranes	3,037 (8.0)	194 (9.0)	1.1 (1.0–1.3)	55 (7.5)	0.9 (0.7–1.2)	19 (6.5)	0.8 (0.5–1.3)	37 (6.2)	0.7 (0.5–1.0)
Induction of labor	714 (1.9)	54 (2.5)	1.2 (0.9–1.7)	13 (1.8)	0.9 (0.5–1.6)	9 (3.1)	1.5 (0.8–3.0)	≤8[b]	0.7 (0.4–1.4)
Cesarean delivery	13,717 (36.2)	773 (35.9)	1.0 (0.9–1.1)	257 (35.1)	1.0 (0.8–1.1)	101 (34.4)	0.9 (0.7–1.2)	219 (36.4)	1.0 (0.8–1.1)

[a]Adjusted for maternal age at delivery, paternal age at delivery, infant sex, infant birth year, hypertension, cardiovascular disease, autoimmune disease, liver disease, diabetes mellitus, renal disease, pulmonary disease, hematologic disease, smoking before pregnancy, alcohol misuse before pregnancy, use of high-risk drugs before pregnancy, paternal nationality, paternal place of residence, paternal income levels (New Taiwan dollars), and paternal occupation.
[b]As per the confidentiality policies of the NHI Research Database, data with sample sizes ≤8 are not displayed in order to protect patient privacy.

high-risk medication use, and cancer therapies. In addition, the considerable sample size of births to male AYA cancer survivors included in the study supports the robustness of our conclusions. However, several limitations should be acknowledged. First, the restriction to live births precludes the analysis of specific outcomes such as intrauterine fetal death and stillbirth. Second, the lack of data on assisted reproductive techniques prevents us from determining whether pregnancies resulted from sperm preservation prior to cancer treatment. This limitation could lead to potential misclassification of treatment groups and an underestimation of risks for certain groups, potentially biasing the ORs toward the null. Third, our definition of lifestyle factors according to the Taiwan National Health Interview Survey, including smoking and alcohol use before pregnancy, may be underestimated and misclassified (25). Fourth, the NHI records date back to 1996 only, which may result in misclassification for patients diagnosed earlier. Fifth, detailed information about CT dose intensity, RT dose and delivery planning, targeted therapies, and immunotherapies was unavailable, limiting the ability to assess the impact of specific treatment regimens on offspring outcomes. Sixth, paternal income, occupation, and medication use might be mediators of the association between paternal AYA cancer history and adverse birth and obstetric outcomes. Adjusting for these factors in the analysis may result in estimating the direct effect of cancer rather than the total effect, potentially underestimating the overall impact of paternal AYA cancer history. Seventh, although marital status is a significant factor influencing adverse birth outcomes (26), this information was not available in our study. This limitation may introduce potential bias in risk evaluation. However, it is important to note that in the construction of the TMCH database, paternal information is derived from spousal data in the Taiwan Birth Registry—a dataset distinct from the TBRS. This characteristic suggests that the majority of children included in this study were born within a marital context, partially mitigating the impact of this limitation. Finally, although additional analyses of particular complications, cancer types, and treatments were conducted, identifying survivor subgroups with significantly increased risks was constrained by limited occurrence numbers. Although some of these increased risks might be attributable to chance findings, we cannot rule out the possibility that certain important significant risks were overlooked. Future investigations with longer follow-up periods could help address this limitation and provide more robust evidence for specific subgroups. Moving forward, tackling

these complex issues could further confirm and expand upon the findings of this study.

In summary, this study found no significant difference in the rates of adverse birth and obstetric outcomes between the offspring born to Taiwanese male AYA cancer survivors and male AYAs without a history of cancer. Further research with longer follow-up periods is warranted, especially as medical practices continue to advance over time in areas like assisted reproductive technology.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

W.-H. Kao: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **Y.-F. Chuang:** Resources, formal analysis, supervision, funding acquisition, methodology, writing–review and editing. **Y.-W. Huang:** Conceptualization, software, formal analysis, funding acquisition, validation, investigation. **P.-J. Chen:** Conceptualization, investigation, methodology. **Y.-C. Liu:** Formal analysis, funding acquisition, investigation, writing–original draft. **C.-C. Wang:** Conceptualization, formal analysis, funding acquisition, investigation, writing–review and editing. **J.-T. Hsu:** Funding acquisition, visualization, methodology, writing–review and editing. **P.-W. Shueng:** Conceptualization, formal analysis, supervision, funding acquisition, methodology, writing–review and editing. **C.-F. Kuo:** Conceptualization, resources, formal analysis, supervision, funding acquisition, visualization, methodology, writing–review and editing.

Disclaimer

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Note

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