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Maternal Comorbidity and Adverse Perinatal Outcomes in Adolescent and Young Adult Cancer Survivors: a Cohort Study

Milli Desai, MD MAS[1,*], **Beth Zhou, MD**[1,*], **Vinit Nalawade, MS**[2], **James Murphy, MD MS**[2], **Nina Veeravalli, MPH**[3], **Henry Henk, PhD**[3], **Cynthia Gyamfi-Bannerman, MD MS**[1], **Brian Whitcomb, PhD**[4], **H. Irene Su, MD MSCE**[1]

[1]Department of Obstetrics, Gynecology, and Reproductive Sciences; University of California, San Diego, 3855 Health Sciences Drive, Dept 0901, La Jolla, CA 92093-0901, USA

[2]Department of Radiation Medicine and Applied Sciences; University of California, San Diego, La Jolla CA

[3]OptumLabs, Minnetonka, MN 55343

[4]Department of Biostatistics and Epidemiology; University of Massachusetts, 433 Arnold House, 715 N Pleasant St, Amherst, MA 01003, USA

Abstract

Objectives: To evaluate risks of preterm birth (PTB) and severe maternal morbidity (SMM) in female adolescent and young adult cancer survivors and assess maternal comorbidity as a potential mechanism. To determine whether associations differ by use of assisted reproductive technology (ART).

Design: Retrospective cohort

Setting: Commercially insured females in the U.S.

Sample: Female with live births from 2000-2019 within a de-identified U.S. administrative health claims dataset

Methods: Log-binomial regression models estimated relative risks of PTB and SMM by cancer status and tested for effect modification. Causal mediation analysis evaluated the proportions explained by maternal comorbidity.

Main Outcome Measures: SMM, PTB

Co-Corresponding Authors: H. Irene Su, MD MSCE, Moores UCSD Cancer Center, 3855 Health Sciences Drive, Dept 0901, La Jolla, CA 92093-0901, hisu@health.ucsd.edu, 858-822-5986; Brian Whitcomb, PhD, 433 Arnold House, 715 N Pleasant St, Amherst, MA 01003, bwhitcom@umass.edu, 413-577-7440.

*Contributed equally

Contribution of authorship

Authors contributed to the conception (MD, JM, BW, HIS), planning (MD, BZ, VN, NV, HH, JM, BW, HIS), carrying out (MD, BZ, VN, NV, BW, HIS), analysis (MD, BZ, VN) and writing up (MD, BZ, VN, NV, HH, JM, BW, HIS) of the work.

Disclosure of interest

JM received consulting fees from Boston Consulting Group, HIS received consulting fees from Ferring Pharmaceuticals. The remaining authors report no conflict of interest.

Details of Ethics Approval

This study used pre-existing, de-identified data and thus was exempt from the University of California San Diego Institutional Review Board approval.[20]

Results: Among 46,064 cancer survivors, 2,440 singleton births, 214 multiple births, and 2,590 linked newborns occurred after cancer. In singleton births, PTB incidence was 14.8% in cancer survivors versus 12.4% in females without cancer (aRR 1.19, 95%CI 1.06-1.34); SMM incidence was 3.9% in cancer survivors versus 2.4% in females without cancer (aRR1.44, 95%CI 1.13-1.83). Cancer survivors had more maternal comorbidities before and during pregnancy; 26% of the association between cancer and PTB and 30% of the association between cancer and SMM was mediated by maternal comorbidities. Tests for effect modification of cancer status on perinatal outcomes by ART were non-significant.

Conclusion: PTB and SMM risks were modestly increased after cancer. Significant proportions of elevated risks may be due to increased comorbidities. ART did not significantly modify the association between AYA cancer and adverse perinatal outcomes. Prevention and treatment of comorbidities provides an opportunity to improve perinatal outcomes among cancer survivors.

Tweetable abstract

A retrospective cohort study shows increased risks of preterm birth & severe maternal morbidity in young female cancer survivors. Part of risks due to increased maternal comorbidities, informing prevention and screening in AYA cancer survivors.

Keywords

Adolescent and young adult cancer; maternal comorbidity; preterm birth; severe maternal morbidity; Adolescent and young adult cancer survivors; perinatal outcomes

Introduction

Adolescent and young adult (AYA) cancer survivors are those diagnosed with cancer between ages 15 and 39. As 5-year survival rates in the U.S. are over 80%, there are 400,000 female AYA cancer survivors of reproductive age.[1] AYA cancer survivors can face more infertility and adverse pregnancy outcomes compared to females without cancer,[2-4] contributing to reproductive distress and family planning decisions.[5-7] Cohort studies report increased preterm birth in young cancer survivors compared to females without cancer, but estimates vary by country.[2, 4, 8, 9]

Data on the magnitude and mechanisms of perinatal risks in female AYA cancer survivors in the U.S. are limited. Preterm birth before 37 weeks (10% of U.S. births) is the leading cause of neonatal mortality and long-term health.[10] In the U.S., the only two sizeable cohort studies approached this question by linking single state cancer registry data to birth certificate data. A prevalence ratio of 1.5 for preterm birth was reported among 2,598 births to AYA cancer survivors relative to controls,[4] while the second study of 2,983 births to young cancer survivors reported a relative risk of 1.2.[11]

A significant but understudied maternal outcome in AYA cancer survivors is severe maternal morbidity (SMM), which encompasses labor and delivery outcomes that result in significant short or long-term consequences to a woman's health.[12] The overall incidence of SMM in the U.S. is around 1.4% among all pregnancies and rising.[13] While pre-eclampsia and

postpartum hemorrhage have been reported among AYA cancer survivors,[9] data on SMM are lacking.

Importantly, little is known about mediators and moderators of increased perinatal risks in this population. AYA cancer survivors can experience late effects of some cancer treatments, such as cardiopulmonary disease,[14] that may increase comorbidities before and during pregnancy. Hence, the International Late Effects of Childhood Cancer Guideline Harmonization Group addresses the need for cardiomyopathy screening and offers recommendations for counselling and surveillance of obstetrical risks of childhood and AYA cancer survivors.[15] While it is unknown if screening for comorbidities risk-stratified by cancer treatments is routine, identification of comorbidities as a mediator would inform screening practices.[15] Assisted reproductive technology (ART) is increasingly used for fertility preservation and infertility treatment in cancer[16] and general populations.[17] ART is itself a risk factor for preterm birth[18] and SMM,[19] but large-scale studies of impact of ART on perinatal risks in cancer survivors are needed.

To address these gaps in knowledge, we used a national administrative claims dataset to estimate the association between AYA cancer and adverse perinatal outcomes of preterm birth and SMM and to investigate mediation by pre-pregnancy and pregnancy maternal comorbidities and moderation by ART. We hypothesized that female AYA cancer survivors experience more maternal comorbidities than females without cancer, and these co-morbidities mediate the effect of prior cancer on preterm birth and SMM.

MATERIALS AND METHODS

Data Source

We used de-identified administrative claims data from the OptumLabs® Data Warehouse (OLDW), which includes medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees. The database contains longitudinal health information for over 200 million enrollees and patients, representing a mixture of ages, ethnicities, and geographical regions across the U.S. Our study period was from 7/1/2000 to 6/30/2019. Diagnoses were obtained using International Statistical Classification of Diseases and Related Health Problems (ICD9/ICD10) diagnostic and procedure codes, Current Procedural Terminology (CPT) codes, Diagnosis Related Group (DRG) codes, and Healthcare Common Procedure Coding System (HCPCS) codes. Since this study involved analysis of pre-existing data that was de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, it was exempt from Institutional Review Board oversight.[20] There was no direct patient or public involvement.

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A UC OptumLabs® Research Award was awarded to the principal investigator, granting access to the OptumLabs® Data Warehouse dataset. OptumLabs® analysts are included as authors on the manuscript.

Study Population

We assembled a cohort of females with at least one pregnancy episode and had continuous insurance enrollment from 30 days before pregnancy start date to 6 weeks after pregnancy end date, allowing for multiple pregnancy episodes per female. We used an algorithm for building live birth cohorts using administrative data that was developed and validated in multiple U.S. and U.K. administrative databases.[21] Claims for pregnancy markers, procedures and outcomes were identified from diagnosis, procedure, DRG, HCPCS, and laboratory test codes (Supplemental Table 1).[21-25] First, pregnancy outcome was assigned to each pregnancy episode. Pregnancy end dates were assigned using the first occurrence of the most reliable outcome code. Pregnancy start dates were then estimated using gestational age claims and pregnancy markers. Live birth episodes were retained for this analysis. We linked mothers and newborns by matching on the offspring's earliest date of insurance coverage within 10 days of the mother's live birth claims code.[26] Mother-to-infant linkage was successful for 90% of live births and did not differ by maternal cancer status. Mothers without a matched infant were retained in the dataset. Plurality was determined by number of infants matched to each pregnancy episode. (Supplemental Table 1).

We assembled a cohort of female AYA cancer survivors querying for cancer codes (Supplemental Table 2),[27] excluding non-melanoma skin. We required ≥ 2 diagnostic codes pertaining to the same cancer site within 12 months.[28] To identify new cancer diagnoses, we required an observed 6-month period of continuous insurance enrollment without another cancer diagnosis prior to the index cancer diagnosis claim date. We retained those of AYA age (15-39) at first cancer diagnosis claim.

Merging the pregnancy and AYA cancer survivor cohorts, we generated a cohort of AYA cancer patients and females without AYA cancer who delivered live births (eFigure 1). For live births in AYA cancer survivors, pregnancy start dates that occurred after the index cancer diagnosis claims date were considered exposed. We retained the first live birth after cancer diagnosis for AYA cancer survivors and the first live birth episode in the dataset for each female without cancer that occurred between the ages 15-50 years of age.

Covariates

Covariates include ART (Supplemental Table 3),[29, 30] cancer treatment variables such as chemotherapy (Supplemental Table 4) and radiation (Supplemental Table 5) prior to the estimated start date of pregnancy, maternal age at delivery(15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-50), maternal comorbidities before and during pregnancy,[31] race/ethnicity (Asian, Black, Hispanic, White, Unknown), year of birth (2000-2004, 2005-2009, 2010-2014, 2015-2020), income (<$40,000, $40,000-74,999, $75,000-124,999, $125,000-199,999, $200,000+, unknown), and education (<12th grade, high school diploma, < bachelor degree, bachelor degree +, unknown). The Maternal Comorbidity Index is a validated tool derived in administrative health claims data to summarize maternal comorbidities occurring up to 6 months before pregnancy and through pregnancy by attributing weights into a numerical score that predicts maternal end-organ damage at delivery or within 30 days postpartum, e.g., severe pre-eclampsia and asthma (Supplemental Table 6).[32]

Outcomes

The primary outcomes were preterm birth and severe maternal morbidity (SMM) during labor and delivery. Preterm birth was defined as birth before 37 weeks of gestation (Supplemental Table 7).[23, 24] As defined by the CDC,[33] SMM was any of 21 indicators during delivery hospitalizations, e.g., disseminated intravascular coagulation and hysterectomy (Supplemental Table 8). Since blood transfusions account for highest proportion of SMM events, we report this outcome including and without transfusion.[12] Maternal and neonatal death were obtained from death records in the dataset.

Statistical Analysis

The exposure was AYA cancer, and the outcomes were preterm birth and SMM. Descriptive characteristics were calculated using frequency and percentages and compared by exposure group Student's t-test or Chi-square test of proportions, as appropriate. Distributions of continuous variables were assessed for normality and reported as mean±SD. Due to skewed distribution, the Maternal Comorbidity Index was log-transformed for analysis. Analysis was stratified by singleton versus multiple live birth, because of known effect modification by pregnancy plurality.[34]

To compare differences in maternal characteristics between births for exposed and unexposed females, we used log-binomial regression models to estimate risk ratios (RR) and 95% confidence intervals (CI) for the outcomes of interest with adjustment for potential confounders (Model 1). We tested for effect modification based on p-values from cross-product terms in regression models. Maternal comorbidities were hypothesized mediators, or causal intermediates, of the relationship between AYA cancer and adverse perinatal outcomes (Model 2). Mediation analysis was undertaken to obtain estimates accounting for the mediator and to estimate the proportion mediated by comorbidities, accounting for potential interactions and non-linear relationships.[35]

Mediation analysis via a counterfactual framework was conducted using PROC CAUSALMED in SAS[36], and GLM regression models were analyzed in R. Subgroup analyses were performed: 1) excluding gynecological cancers because of known associations between these and preterm birth, and 2) restricting the study period from 2010 to 2019 to considering temporal advances in cancer and perinatal care. All tests of significance were two-tailed, and alpha was 0.05.

RESULTS

We identified 1,563,899 pregnancy episodes in 1,321,312 females. Among females without a history of cancer, the cohort included 1,251,935 first singleton live births, 71,618 first multiple live births, and 1,212,710 linked newborns. Among 46,064 female cancer survivors, the cohort included 2,440 first singleton live births, 214 multiple live births, and 2,590 linked newborns (Supplemental Figure 1). Among cancer survivors, the most common cancer types were thyroid (21.8%), melanoma (20.0%), and breast (16.7%) (Table 1). Compared to those without a history of cancer, cancer survivors were older at delivery,

had more comorbidities before and during pregnancy and were more likely to undergo ART. Cancer survivors had higher incidence of both preterm birth and SMM (Table 1).

In singleton births, the incidence of preterm birth was 14.8% in cancer survivors compared to 12.4% in females without cancer; the incidence of SMM was 3.9% in cancer survivors compared to 2.4% in females without cancer. The most common SMM conditions were cardiopulmonary (1.9% in cancer survivors vs. 1.1% in females without cancer) and end organ injury (1.6% in cancer survivors vs 0.9% in females without cancer) (Supplemental Figure 2). Unadjusted and adjusted relative risks of preterm birth and SMM are depicted in Table 2. Due to the collinearity of race and ethnicity, income, and education, the adjusted regression model with the best fit accounted used race/ethnicity as a covariate. Adjusting for maternal age at delivery, race/ethnicity, chemotherapy, radiation therapy, year of birth, and ART, AYA cancer was associated with 1.19-fold higher risk of preterm birth (95% CI 1.06-1.34) and 1.44-fold higher risk of SMM (95% CI 1.13-1.83) (Model 1, Table 2).

We conducted mediation analysis in order to evaluate maternal comorbidity as a potential mechanism to explain associations between AYA cancer and adverse outcomes. Nearly all comorbidities in the Maternal Comorbidity Index occurred more frequently in cancer survivors compared to females without a history of cancer in both singleton and multiple births (Figure 1). In models for preterm birth and SMM accounting for the Maternal Comorbidity Index as a putative mediator (Model 2, Table 2)., AYA cancer remained significantly associated with preterm birth (aRR 1.21, 95% CI 1.06-1.39) and SMM (aRR 1.40, 95% CI 1.09-1.79). Using this approach to estimate indirect and total effects, result of mediation analysis suggested that maternal comorbidities before and during pregnancy explain 26% of the association between AYA cancer and preterm birth and 30% of the association between AYA cancer and SMM.

In multiple births, the incidence of preterm birth was 38.8% in cancer survivors compared to 34.4% in females without cancer; the incidence of SMM was 8.9% in cancer survivors compared to 6.8% in females without cancer. Unadjusted, confounder adjusted (Model 1), and mediation model (Model 2) based relative risks of preterm birth and SMM are depicted in Table 3; no significant associations were observed in cancer survivors relative to the females without cancer.

In adjusted models in singleton births, ART was associated with 1.4-fold and 1.6-fold higher risks of preterm birth and SMM, respectively (Model 2, Table 2). In adjusted models of multiple births, ART was associated with a 2.6-fold and 2.0-fold higher risk of preterm birth and SMM respectively (Model 2, Table 3). Tests for effect modification of cancer status on perinatal outcomes by ART were all non-significant. Initially, these models included covariates (model 2); unadjusted models were also used to maximize statistical power to detect interaction and compare stratum-specific estimates. In these models, the association of AYA cancer with PTB in singletons did not vary significantly (P-interaction=0.12) between ART (RR 1.40, 95% CI 1.05, 1.87) and non-ART (RR 1.27, 95% CI 1.14, 1.41), and similar results were observed among multiple births (RR_{ART} 0.87, 95% CI 0.58, 1.30 vs. $RR_{non\text{-}ART}$ 1.13, 95% CI 0.87, 1.46; P-interaction=0.13). The association of AYA cancer with SMM in singletons also did not vary significantly (P-interaction=0.11) between ART

(RR 2.45, 95% CI 1.56, 3.86) and non-ART (RR 1.48, 95% CI 1.18, 1.85). Similar results were observed among multiple births (RR_{ART} 1.04, 95% CI 0.50, 2.19 vs. $RR_{non\text{-}ART}$ 1.25, 95% CI 0.71, 2.20; P-interaction=0.87).

Two subgroup analyses were undertaken. Excluding gynecological cancers (ovarian, cervical, uterine, other reproductive cancers) because of known associations between these and preterm birth[37], AYA cancer survivors with singletons still had increased risk of preterm birth (aRR 1.14; 95% CI, 1.01-1.29) compared to females without cancer. This association was not significant in multiple births (aRR 0.85, 95% CI, 0.63-1.14). In subgroup analysis restricted to births between 2010 and 2019, AYA cancer's association with preterm birth and SMM and mediation by maternal comorbidity did not materially change (data not shown).

DISCUSSION

Main findings

In the largest U.S. cohort of births to female AYA cancer survivors to date, this study shows modestly increased risks of preterm birth and severe maternal morbidity in singleton births to AYA cancer survivors compared to those births to females without cancer, findings which support overall reassuring maternal and offspring outcomes of pregnancies after cancer. AYA cancer survivors had more comorbidities before and during pregnancy. As results suggest that approximately 30% of preterm birth and SMM may be due to maternal comorbidities, the findings shed light on the potential mechanisms through which these adverse perinatal outcomes occur and demonstrate a heightened need for clinical screening and prevention of comorbidities before and during pregnancy in reproductive-aged cancer survivors.

Assessment of comorbidities prior to and during pregnancy in this study provided new information on perinatal risks after cancer and is important because these conditions are determinants of SMM and mortality.[38] Nearly all maternal comorbidities before and during pregnancy occurred more frequently in AYA cancer survivors than females without cancer, including cardiopulmonary and renal diseases that are known late effects of some cancer treatments.[14] Indeed, we observed that prior chemotherapy (but not radiation) was significantly associated with higher comorbidity index (data not shown). Because mediation analysis suggests that maternal comorbidities are in the pathway between prior cancer and preterm births, the clinical implication of our work is the need for fidelity to preconception and prenatal surveillance (e.g., for hypertension[39] and renal disease[40]) and/or interventions (e.g., aspirin for pre-eclampsia prevention[41]) in AYA cancer survivors.

Severe maternal morbidity, which comprises life-threatening labor and delivery outcomes that result in significant short- or long-term consequences to a female's health, occurred at a 1.4-fold higher frequency in births to AYA cancer survivors than those to females without cancer. The single additional report on SMM in childhood and adolescent cancer survivors and matched females without cancer from the Ontario cancer and obstetrical registries, observed a relative risk of 2.3 (95% CI 1.5-3.6).[42] Beyond this, little is known about the incidence of this CDC-defined composite maternal outcome in AYA cancer survivors, but increased risks in AYA cancer survivors is consistent with the attribution of rising rates of SMM in the U.S. to increasing incidence of chronic diseases in females.[43] Because absolute

rates are low, we are limited in further delineation of cancer treatment-related risks of severe maternal morbidity, which will require pooling large datasets such as the one used in the current study.

Our observation of increased preterm birth risk is consistent with but of a lower magnitude than prior studies in female childhood and AYA cancer survivors. In a meta-analysis of cohorts from Europe, Australia and the U.S.,[8] preterm birth rates globally are highly variable, supporting generating evidence by geographic population. We compare our findings to the two other population-based U.S. cohorts. Linked North Carolina cancer registry and birth certificate data showed a prevalence ratio of 1.52 (95% CI 1.34-1.71) comparing 2,598 singleton births to AYA cancer survivors with 12,990 singleton births to women without cancer, while linked Massachusetts cancer registry and vital records showed a relative risk of 1.2 (95% CI 1.07-1.32) comparing nearly 3,000 births to cancer survivors of unspecified diagnosis age to births in females without cancer.[11]

Approximately 30% of preterm birth and SMM were attributable to maternal comorbidities. Other potential mediators of these outcomes could be factors such as older maternal age, pre-pregnancy obesity, race, and prior preterm birth.[10, 44, 45] Certainly, many preterm births and SMM remain unexplained.

As expected, multiple births resulted in significantly higher risks of adverse perinatal outcomes, but this was not different by cancer status. ART was a significant contributor to multiple births. As ART techniques improve over time, guideline-based clinical practice[46] needs to continue to improve on single embryo transfers to decrease the known complications of multiple birth.[47] While ART use did not statistically significantly modify the association between AYA cancer and adverse perinatal outcomes, replicative work on SMM with a larger cohort is needed.

Strengths and Limitations

Using the validated and weighted Maternal Comorbidity Index[31, 48], capture of the range of maternal comorbidities was a distinct advantage of using health claims data, as these data capture utilization before, during and post-delivery as well as across multiple health care delivery sites accessed by each patient.[49] In comparison, prior studies used self-report, birth certificate and/or hospital discharge data for birth outcomes and related morbidity and were limited in identifying the full range of comorbidities that precede and occur during pregnancy.[3, 4] Results of our mediation analysis helps explain why AYA cancer survivors have more adverse perinatal outcomes, and illustrates potential use of this analytic approach for future research aimed at improving outcomes in cancer survivors.

We note several limitations. First, prior cancer remained associated with adverse outcomes in singleton births, after adjusting for broad chemotherapy or radiation exposures and comorbidities, leaving unanswered why cancer itself would be related to these outcomes. One potential reason is iatrogenic delivery, which cannot be accurately captured in administrative data. Restricting to commercial insurance enrollees due to the nature of the dataset excludes women with Medicaid (which provides coverage for large proportions of cancer survivors and pregnant individuals in the U.S.[50]). As social determinants

of health such as education, income and race are associated with insurance type and contribute to disparities to both cancer and perinatal outcomes,[51-53] the generalizability of our data is limited to commercially insured individuals. Enrollees may not have been insured throughout the course of previous cancer treatment, leading to misclassification as unexposed and represent a bias toward the null. Misclassification may also have resulted from those enrollees who used cash or different insurance to undergo ART than during pregnancy but likely to be non-differential. As we relied on billing codes (ICD, CPT, DRG, etc.) to identify exposures, covariates, and outcomes, misclassification could have occurred but also anticipated to be non-differential by cancer status. While both severity of preterm births (<28 weeks, <32 weeks) and spontaneous versus iatrogenic preterm births are outcomes of interest, claims cannot accurately capture them. Existing billing codes are not specific to anatomic region for radiation, limiting specificity of radiation exposure. Due to using both ICD-9 and ICD-10-CM/PCS codes, potential disruptions in observed rates relating to the coding transition and coding errors could contribute to misclassification bias. Confounders including smoking, obesity, and prior preterm birth are not reliable in health claims data and thus could not be included. Finally, there may be detection bias of comorbidities and outcomes in AYA cancer survivors that contributed to our findings.

Conclusion

In the U.S., maternal morbidity and mortality is increasing, and there is a need to target populations at higher risks. Taken together, our findings suggest that tackling adverse perinatal outcomes in AYA cancer survivors involves mitigating pre- and intra-pregnancy comorbidities this population experiences as a result of cancer and related treatment. Our findings are clinically significant, because they inform counseling, screening, and medical management to prevent and manage both comorbidities as well as the adverse perinatal outcomes of preterm birth and severe maternal morbidity. Next, detailing which specific cancer treatments, beyond broad categories of chemotherapy, radiation, and surgery, are related to which maternal comorbidity is needed to prioritize research and clinical screening and surveillance. Future studies that leverage claims data to measure more detailed exposures may be feasible and valid.[54-56]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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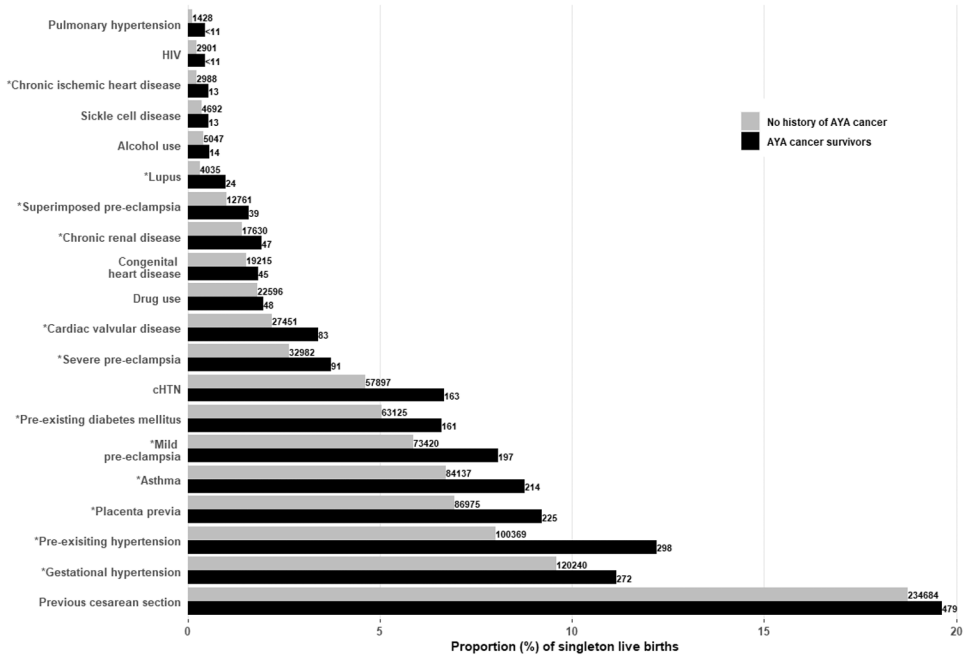

Figure 1:
Maternal comorbidities by AYA cancer status. *indicates $p<0.05$

Table 1:

Comparison of baseline characteristics and perinatal outcomes of singleton and multiple live births by history of AYA cancer*

	Singleton live births			*Multiple live births*		
	AYA cancer survivors N=2,440 births	**No history of AYA cancer N=1,251,935 births**	***P*-value**	**AYA cancer survivors N=214 births**	**No history of AYA cancer N=71,618 births**	***P*-value**
Maternal age at delivery (No. %)						
15-19	19 (0.8)	36,037 (2.9)		0 (0)	256 (0.4)	
20-24	103 (4.2)	132,144 (10.6)		< 11 (<5.1)	3,654 (5.1)	
25-29	436 (17.9)	339,108 (27.1)		33 (15.4)	17,663 (24.7)	
30-34	> 888 (>36.4)	437,769 (35.0)	<0.0001	> 78 (>36.4)	27,937 (39.0)	0.0005
35-39	782 (32.1)	239,162 (19.1)		69 (32.2)	17,128 (23.9)	
40-44	201 (8.2)	58,490 (4.7)		23 (10.7)	4,327 (6.0)	
45-50	< 11 (<0.5)	9,225 (0.7)		0 (0)	653 (0.9)	
Year of birth (No. %)						
2000-2004	259 (10.6)	270,091 (21.6)		28 (13.1)	11,112 (15.5)	
2005-2009	733 (30.0)	374,240 (29.9)	<0.0001	68 (31.8)	25,297 (35.3)	0.37
2010-2014	799 (32.7)	326,221 (26.1)		73 (34.1)	21,936 (30.6)	
2015-2020	649 (26.6)	281,383 (22.5)		45(21.0)	13,273 (18.5)	
Race/ethnicity† (No. %)						
Asian	152 (6.2)	98,979 (7.9)		< 11 (<5.1)	5,212 (7.3)	
Black	266 (10.9)	161,510 (12.9)		29 (13.6)	8,005 (11.2)	
Hispanic	338 (13.9)	162,566 (13.0)	<0.0001	26 (12.1)	8,740 (12.2)	0.01
White	1,131 (46.4)	580,582 (46.4)		> 89 (>41.6)	35,338 (49.3)	
Unknown	553 (22.7)	248,298 (19.8)		59 (27.6)	14,323 (20.0)	
Income (No. %)						
<$40,000	390 (16.0)	216,735 (17.3)		32 (15.0)	10,217 (14.3)	
$40,000-74,999	551 (22.6)	265,411 (21.2)		38 (17.8)	15,931 (22.2)	
$75,000-124,999	605 (24.8)	242,517 (19.4)	<0.0001	54 (25.2)	15,694 (21.9)	0.32
$125,000-199,999	298 (12.2)	119,066 (9.5)		27 (12.6)	8,443 (11.8)	
$200,000+	173 (7.1)	65,571 (5.2)		20 (9.3)	4,919 (6.9)	
Unknown	423 (17.3)	342,635 (27.4)		43 (20.1)	16,414 (22.9)	
Education (No. %)						
< 12th grade	53 (2.2)	33,358 (2.7)		< 11 (<5.1)	1,724 (2.4)	
High school diploma	922 (37.8)	488,657 (39.0)		68 (31.8)	26,524 (37.0)	
< Bachelor degree	1,136 (46.6)	547,973 (43.8)	<0.0001	> 95 (>44.4)	32,918 (46.0)	0.33
Bachelor degree +	308 (12.6)	136,661 (10.9)		29 (13.6)	9,082 (12.7)	
Unknown	21 (0.9)	45,286 (3.6)		< 11 (<5.1)	1,370 (1.9)	
Maternal Comorbidity Index (mean score±SD)	1.8±2.3	1.2±1.7	<0.0001	3.2±2.9	2.2±2.4	<0.0001
Maternal Comorbidity Index (median, IQR)	1.0 (0, 3.0)	1.0 (0, 2.0)	<0.0001	2.5 (1.0, 4.0)	2.0 (0, 3.0)	<0.0001

Assisted reproductive technology use (No. %)	181 (7.4)	43,992 (3.5)	<0.0001	43 (20.1)	8,369 (11.7)	0.0002
Cancer type (No. %)						
Thyroid	541 (22.2)	-		38 (17.8)	-	
Melanoma	479 (19.6)	-		53 (24.8)	-	
Breast	404 (16.6)	-		38 (17.8)	-	
Leukemia	184 (7.5)	-		16 (7.5)	-	
Non-Hodgkin's Lymphoma	125 (5.1)	-		11 (5.1)	-	
Gastrointestinal	56 (2.3)	-		< 11 (<5.1)	-	
Hodgkin's Lymphoma	125 (5.1)	-		13 (6.1)	-	
Ovarian	106 (4.3)	-		< 11 (<5.1)	-	
Central nervous system	78 (3.2)	-		< 11 (<5.1)	-	
Cervical	71 (2.9)	-		< 11 (<5.1)	-	
Bone	46 (1.9)	-		< 11 (<5.1)	-	
Renal	45 (1.8)	-		< 11 (<5.1)	-	
Sarcoma	39 (1.6)	-		< 11 (<5.1)	-	
Lung	28 (1.1)	-		0 (0)	-	
Other reproductive	13 (0.5)	-		< 11 (5.1)	-	
Uterine	22 (0.9)	-		0 (0)	-	
Chemotherapy (No. %)	583 (23.9)	-		62 (29.0)	-	
Radiation (No. %)	162 (6.6)	-		14(6.5)	-	
	Singleton birth outcomes			***Multiple birth outcomes***		
Preterm birth (No. %)	548 (14.8)	155,296 (12.4)	<0.0001	83 (38.8)	24,683 (34.4)	0.21
Severe Maternal Morbidity (SMM) (No. %)	96 (3.9)	29,666 (2.4)	<0.0001	<22 (<10.3)	4,866 (6.8)	0.13
SMM without blood transfusion (No. %)	73 (3.0)	23,007 (1.8)	<0.0001	11 (5.1)	3,939 (5.5)	0.94

*To maintain the de-identified nature of the OptumLabs Data Warehouse and in-line with CMS's policy to minimize the risk of re-identifying an individual, all summary tables/graphs may not display cells on identifiable patient attributes with fewer than 11 patients.

†Race and ethnicity is assigned by an external vendor who uses a rule-based system that combines analysis of first names, middle names, surnames, and surname prefixes and suffixes with geographic criteria. Optum Labs then assigns these ethnicity values into one of five compliance-determined race code values: Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, and unknown.

Table 2:

Unadjusted, adjusted (Model 1), and mediation model (Model 2)-based relative risks (RR, 95% CI) of preterm birth and severe maternal morbidity in singleton live births

	Preterm Birth			Severe Maternal Morbidity		
	Unadjusted	**Model 1***	**Model 2†**	**Unadjusted**	**Model 1***	**Model 2†**
AYA cancer	1.31 (1.19, 1.44) p<0.001	1.19 (1.06, 1.34) p=0.003	1.21 (1.06, 1.39) p=0.006	1.66 (1.36, 2.03) p<0.001	1.44 (1.13, 1.83) p=0.003	1.40 (1.09, 1.79) p=0.009
Maternal Comorbidity Index	1.05 (1.05, 1.05), p<0.001	--	1.05 (1.05, 1.06) p<0.001	1.10 (1.10, 1.11) p<0.001	--	1.10 (1.10, 1.11) p<0.001
ART	1.49 (1.46, 1.53) p<0.001	1.39 (1.36, 1.42) p<0.001	1.40 (1.36, 1.43) p<0.001	1.87 (1.78, 1.96) p<0.001	1.75 (1.67, 1.83) p<0.001	1.60 (1.53, 1.68) p<0.001
Age						
15-19	0.52 (0.50, 0.54) p<0.001	0.52 (0.49, 0.54) p<0.001	0.50 (0.47, 0.52) p<0.001	0.79 (0.73, 0.86) p<0.001	0.76 (0.70, 083) p<0.001	0.81 (0.74, 0.88) p<0.001
20-24	0.76 (0.75, 0.78) p<0.001	0.76 (0.74, 0.77) p<0.001	0.74 (0.72, 0.75) p<0.001	0.91 (0.87, 0.95) p<0.001	0.89 (0.85, 0.93) p<0.001	0.91 (0.87, 0.95) p<0.001
25-29	reference	reference	reference	reference	reference	reference
30-34	1.07 (1.05, 1.08) p<0.001	1.06 (1.05, 1.08) p<0.001	1.05 (1.03, 1.06) p<0.001	1.10 (1.07, 1.14) p<0.001	1.11 (1.07, 1.14) p<0.001	1.06 (1.03, 1.10) p<0.001
35-39	1.16 (1.14, 1.17) p<0.001	1.15 (1.13, 1.17) p<0.001	1.12 (1.10, 1.13) p<0.001	1.29 (1.25, 1.34) p<0.001	1.28 (1.24, 1.32) p<0.001	1.18 (1.14, 1.22) p<0.001
40-44	1.28 (1.25, 1.31) p<0.001	1.25 (1.22, 1.28) p<0.001	1.21 (1.18, 1.24) p<0.001	1.71 (1.63, 1.79) p<0.001	1.63 (1.56,1.71) p<0.001	1.47 (1.40, 1.54) p<0.001
45-50	1.11 (1.05,1.17) p=0.004	1.06 (1.00, 1.12) p=0.06	1.00 (0.94, 1.06) p=0.96	1.66 (1.49, 1.86) p<0.001	1.55 (1.39, 1.73) p<0.001	1.41 (1.26, 1.58) p<0.001
Race/ethnicity #						
White	reference	reference	reference	reference	reference	reference
Asian	1.25 (1.22, 1.27) p<0.001	1.16 (1.14, 1.18) p<0.001	1.23 (1.20, 1.25) p<0.001	1.02 (0.98, 1.07) p=0.39	0.98 (0.94, 1.03) p=0.50	1.04 (1.00, 1.09) p=0.08
Black	1.17 (1.15, 1.19) p<0.001	1.16 (1.15, 1.18) p<0.001	1.16 (1.14, 1.17) p<0.001	1.29 (1.25, 1.33) p<0.001	1.31 (1.27, 1.36) p<0.001	1.26 (1.21, 1.30) p<0.001
Hispanic	1.10 (1.08, 1.12) p<0.001	1.10 (1.08, 1.11) p<0.001	1.10 (1.08, 1.12) p<0.001	1.07 (1.03, 1.11) p<0.001	1.09 (1.05, 1.13) p<0.001	1.07 (1.04, 1.11) p<0.001
Unknown	1.01 (1.00, 1.02) p=0.18	1.01 (0.99, 1.02) p=0.37	1.00 (0.99, 1.02) p=0.59	1.02 (0.99, 1.05) p=0.25	1.02 (0.99, 1.05) p=0.20	1.02 (0.99, 1.05) p=0.30
Year of birth						
2000-2004	reference	reference	reference	reference	reference	reference
2005-2009	1.26 (1.24, 1.28) p<0.001	1.23 (1.22, 1.25) p<0.001	1.22 (1.20, 1.24) p<0.001	1.01 (0.98, 1.04) p=0.53	0.99 (0.95, 1.02) p=0.42	0.92 (0.89, 0.95) p<0.001
2010-2014	1.29 (1.27, 1.51) p<0.001	1.45 (1.42, 1.47) p<0.001	1.46 (1.44, 1.48) p<0.001	1.16 (1.12, 1.20) p<0.001	1.11 (1.08, 1.15) p<0.001	1.03 (0.99, 1.06) p=0.12
2015-2019	1.28 (1.26, 1.30) p<0.001	1.23 (1.21, 1.25) p<0.001	1.23 (1.21, 1.25) p<0.001	0.95(0.91, 0.98) p=0.002	0.90 (0.87, 0.93) p<0.001	0.84 (0.81, 0.87) p<0.001
Chemotherapy	1.37 (1.12, 1.67) p=0.002	0.95 (0.75, 1.20) p=0.66	0.92 (0.71, 1.19) p=0.52	2.03 (1.40, 2.93) p<0.001	1.11 (0.70, 1.75) p=0.67	1.07 (0.67,1.71) p=0.78
Radiation therapy	1.54 (1.08, 2.19) p=0.02	1.17 (0.80, 1.72) p=0.41	1.21 (0.79, 1.86) p=0.37	2.34 (1.22, 4.50) p=0.01	1.32 (0.65, 2.69) p=0.45	1.33 (0.63, 2.78) p=0.45

* Model 1 adjusts for maternal age, race/ethnicity, year of birth, chemotherapy, radiation therapy

[†]Model 2: Model 1 + Maternal Comorbidity Index as mediator + mediator-cancer interaction

[#]Race and ethnicity is assigned by an external vendor who uses a rule-based system that combines analysis of first names, middle names, surnames, and surname prefixes and suffixes with geographic criteria. Optum Labs then assigns these ethnicity values into one of five compliance-determined race code values: Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, and unknown.

Table 3:

Unadjusted, adjusted (Model 1), and mediation model (Model 2)-based relative risks (RR, 95% CI) of preterm birth and severe maternal morbidity in multiple live births

	Preterm Birth			Severe Maternal Morbidity		
	Unadjusted	**Model 1***	**Model 2†**	**Unadjusted**	**Model 1***	**Model 2†**
AYA cancer	1.13 (0.91, 1.40) p=0.28	0.89 (0.67, 1.19) p=0.44	0.72 (0.50, 1.04) p=0.08	1.31 (0.83, 2.05) p=0.24	0.59 (0.27, 1.32) p=0.20	0.44 (0.15, 1.25) p=0.13
Maternal Comorbidity Index	1.17(1.17, 1.18), p<0.001	--	1.22 (1.21, 1.22) p<0.001	1.30, 1.28, 1.32) p<0.001	--	1.29 (1.27, 1.31) p<0.001
ART	2.09 (2.03, 2.15) p<0.001	1.97 (1.91, 2.03) p<0.001	2.58 (2.46, 2.72) p<0.001	2.77 (2.60, 2.95) p<0.001	2.54 (2.37, 2.71) p<0.001	2.00 (1.86, 2.16) p<0.001
Age						
25-29	reference	reference	reference	reference	reference	reference
15-19	0.77 (0.59, 0.99) p=0.04	0.80 (0.61, 1.03) p=0.08	0.86 (0.63, 1.18) p=0.36	0.92 (0.53, 1.59) p=0.76	0.95 (0.55, 1.64) p=0.85	1.15 (0.65, 2.04) p=0.63
20-24	0.87 (0.82, 0.94) p<0.001	0.89 (0.83, 0.96) p=0.002	0.95 (0.74, 1.04) p=0.25	0.86 (0.74, 1.02) p=0.08	0.89 (0.76, 1.04) p=0.15	0.98 (0.83, 1.16) p=0.80
30-34	1.14 (1.11, 1.18) p<0.001	1.09 (1.05, 1.13) p<0.001	1.03 (0.99, 1.08) p=0.16	1.14 (1.06, 1.24) p<0.001	1.07 (0.99, 1.16) p=0.08	0.98 (0.90, 1.06) p=0.62
35-39	1.33 (1.28, 1.38) p<0.001	1.20 (1.16, 1.25) p<0.001	1.11 (1.06, 1.16) p<0.001	1.43 (1.43, 1.56) p<0.001	1.25 (1.15, 1.35) p<0.001	1.07 (0.98, 1.16) p=0.16
40-44	1.45 (1.38, 1.53) p<0.001	1.20 (1.14, 1.27) p<0.001	1.07 (0.99, 1.15) p=0.09	1.87 (1.67, 2.09) p<0.001	1.43 (1.28, 1.60) p<0.001	1.20 (1.07, 1.36) p=0.003
45-50	2.21 (2.00, 2.44) p<0.001	1.56 (1.41, 2.73) p=0.002	1.65 (1.53, 2.17) p<0.001	3.60 (3.00, 4.32) p<0.001	2.22 (1.84, 2.68) p<0.001	1.83 (1.49, 2.26) p<0.001
Race/ethnicity #						
White	reference	reference	reference	reference	reference	reference
Asian	1.12 (1.07, 1.17) p<0.001	1.04 (0.99, 1.09) p=0.10	1.17 (1.10, 1.25) p<0.001	1.03 (0.93, 1.15) p=0.55	0.95 (0.85, 1.06) p=0.36	1.00 (0.89, 1.13) p=0.97
Black	1.06 (1.02, 1.10) p=0.005	1.09 (1.05, 1.14) p<0.001	1.08 (1.02, 1.14) p=0.008	1.03 (0.94, 1.13) p=0.56	1.08 (0.99, 1.19) p=0.09	1.03 (0.93, 1.13) p=0.58
Hispanic	0.95 (0.91, 0.99) p=0.01	0.97 (0.93, 1.01) p=0.14	0.97 (0.91, 1.02) p=0.21	0.86 (0.78, 0.95) p=0.002	0.90 (0.82, 0.99) p=0.03	0.90 (0.82, 1.00) p=0.05
Unknown	1.06(1.03, 1.10) p<0.001	1.04 (1.01, 1.08) p=0.02	1.03 (0.99, 1.08) p=0.17	1.07 (1.00, 1.15) p=0.07	1.05 (0.98, 1.13) p=0.18	1.02 (0.95, 1.11) p=0.55
Year of birth						
2000-2004	reference	reference	reference	reference	reference	reference
2005-2009	0.87 (.84, 0.91) p<0.001	0.88 (0.85, 0.91) p<0.001	0.82 (0.78, 0.86) p<0.001	0.82 (0.75, 0.89) p<0.001	0.83 (0.76, 0.90) p<0.001	0.83 (0.76, 0.90) p<0.001

	Preterm Birth			Severe Maternal Morbidity		
	Unadjusted	**Model 1***	**Model 2†**	**Unadjusted**	**Model 1***	**Model 2†**
2010-2014	0.97 (0.92, 1.00) p=0.03	0.91 (0.88, 0.94) p<0.001	0.86 (0.82, 0.91) p<0.001	0.91 (0.83, 0.98) p=0.02	0.84 (0.77, 0.91) p<0.001	0.83 (0.76, 0.91) p<0.001
2015-2019	0.99 (0.95, 1.03) p=0.58	0.93 (0.89, 0.97) p<0.001	0.88 (0.83, 0.93) p<0.001	0.83 (0.74, 0.89) p<0.001	0.75 (0.68, 0.82) p<0.001	0.72 (0.65, 0.80) p<0.001
Chemotherapy	1.69 (1.22, 2.34) p=0.002	1.37 (0.87, 2.15) p=0.17	1.96 (0.98, 3.91) p=0.06	3.09 (1.79, 5.32) p<0.001	3.96 (1.49, 10.53) p=0.006	4.79 (1.64, 14.0) p=0.004
Radiation therapy	1.66, 0.83 (3.31) p=0.15	1.18 (0.55, 2.51) p=0.67	2.04 (0.51, 8.18) p=0.31	1.05 (0.15, 7.46 (0.96)	0.39 (0.05, 2.98) p=0.36	0.28 (0.03, 2.63) p=0.27

*Model 1 adjusts for maternal age, race/ethnicity, year of birth, chemotherapy, radiation therapy

†Model 2: Model 1 + Maternal Comorbidity Index as mediator + mediator-cancer interaction

#Race and ethnicity is assigned by an external vendor who uses a rule-based system that combines analysis of first names, middle names, surnames, and surname prefixes and suffixes with geographic criteria. Optum Labs then assigns these ethnicity values into one of five compliance-determined race code values: Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, and unknown.