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Hypertensive Disorders of Pregnancy Among Women With A History of Leukemia or Lymphoma

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Author Contributions

Sonia T. Anand – I declare that I participated in the conceptualization, formal analysis, writing of the original draft, review and editing of the draft, and I have seen and approved the final version. I have the following conflicts of interest: I received the grant from National Cancer Institute under Grant number P30 CA086862-18S6 that supported this research.

Kelli K. Ryckman – I declare that I participated in conceptualization, funding acquisition, project administration, supervision, review and editing of the draft, and I have seen and approved the final version. I have the following conflicts of interest: I received the grant from National Cancer Institute under Grant number P30 CA086862-18S6 that supported this research.

Rebecca J. Baer – I declare that I participated in data curation, review and editing of the draft, and I have seen and approved the final version. I have no conflicts of interest.

Mary E. Charlton – I declare that I participated in conceptualization, review and editing of the draft, and I have seen and approved the final version. I have no conflicts of interest.

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Elizabeth A. Chrischilles – I declare that I participated in conceptualization, project administration, supervision, review and editing of the draft, and I have seen and approved the final version. I have no conflicts of interest.

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Abstract

Objective: Hypertension during pregnancy can adversely affect maternal and fetal health. This study assessed whether diagnosis of leukemia or lymphoma prior to pregnancy is associated with hypertensive disorders of pregnancy including gestational hypertension, preeclampsia and eclampsia.

Study design: A cross-sectional study used two statewide population-based datasets that linked birth certificates with sources of maternal medical history: hospital discharges in California and Surveillance, Epidemiology, and End Results (SEER) cancer registry data in Iowa. Birth years included 2007–2012 in California and 1989–2018 in Iowa.

Main outcome measures: Primary outcome measure was hypertension in pregnancy measured from combined birth certificate and hospital diagnoses in California (for gestational hypertension, preeclampsia, or eclampsia) and birth certificate information (gestational hypertension or eclampsia) in Iowa.

Results: After adjusting for maternal age, race, education, smoking, and plurality, those with a history of leukemia/lymphoma were at increased risk of hypertensive disorders of pregnancy in Iowa (odds ratio (OR) = 1.86; 95% CI 1.07–3.23), but not in California (OR =1.12; 95% CI 0.87–1.43). In sensitivity analysis restricting to more severe forms of hypertension in pregnancy (preeclampsia and eclampsia) in the California cohort, the effect estimate increased (OR = 1.29; 95% CI 0.96–1.74).

Conclusion: In a population-based linked cancer registry-birth certificate study, an increased risk of hypertensive disorders of pregnancy was observed among leukemia or lymphoma survivors. Findings were consistent but non-significant in a second, more ethnically diverse study population with less precise cancer history data. Improved monitoring and surveillance may be warranted for leukemia or lymphoma survivors throughout their pregnancies.

Keywords

gestational hypertension; leukemia; lymphoma; pregnancy; preeclampsia; eclampsia

INTRODUCTION

Leukemia and lymphoma are two of the top cancers affecting children, adolescent and young adult patients (AYA). With improved treatments and therapies, the estimated 5-year survival rate for most cancer sites is over 80% for adolescent and young adult patients (1). The percent surviving 5-years is 62.7% for leukemia patients, 72.0% for non-Hodgkin lymphoma, and 86.6% for Hodgkin lymphoma, based on 2009–2015 data (2). With long-term survival, concerns regarding late-effects of cancer treatments have been raised. In studies assessing the health needs of adolescent and young adult cancer survivors, one of the top priority needs was more information regarding fertility, reproductive outcomes, and sexuality (3, 4). About 75% of cancer survivors, the majority being childhood cancer survivors, express interest in having a child after a cancer diagnosis and treatment (5, 6).

Late-effects of treatment, especially health of offspring, is a major concern for leukemia and lymphoma cancer survivors with capacity for pregnancy (7). Healthy pregnancies require a normally functioning uterus, an intact hypothalamic-pituitary-ovarian axis, and an adequate ovarian follicle reserve (8). However, cancer treatments such as radiotherapy or chemotherapy, used when treating leukemia and lymphoma, can damage and alter functions of these reproductive organs. Radiotherapy can potentially damage the vagina, uterus, and ovaries and thus lead to vaginal stenosis and fibrosis, uterine vasculature and musculature damage, and premature ovarian insufficiency (9–13). Chemotherapy can lead to ovarian failure due to potentially being gonadotoxic. Cancer surgery can cause damage to reproductive structures and impair reproductive health if reproductive organs are removed (9, 13). The level of damage varies based on type of treatment, drugs and dosage used, stage of diagnosis, and age at diagnosis. Cancer survivors who had chemotherapy are at higher risk for miscarriages and preterm deliveries compared to other cancer treatments, such as radiation and surgery (14–16).

Additional late-effects of leukemia and lymphoma include potentially developing gestational hypertension. Treatments for leukemia and lymphoma include drugs such as platinum agents and anthracyclines. Platinum agents can lead to renal impairments; anthracyclines produce free radicals, and these toxic effects increase the risk for gestational hypertension (17–20). Few studies assess the risk of preeclampsia and gestational hypertension with cancer (21, 22). These studies were conducted outside the United States, had small sample sizes, and inadequate ascertainment of gestational hypertension. The primary objective of our study is to assess whether a diagnosis of cancer prior to pregnancy is associated with hypertension during pregnancy including gestational hypertension, preeclampsia and/or eclampsia in two US states.

METHODS

Data Source and Linkages

Two administrative data sources we had access to were included from California and Iowa. For California, a linked dataset maintained by the California Office of Statewide Health Planning and Development (OSHPD) was used. The dataset information includes births in California from 2007 to 2012 linked to hospital discharge, birth certificate (BC), and death records data from birth to one year. This encompasses all records for mother and infant from one year before birth to one year after birth. Birth certificates also include information on prenatal care and select antenatal conditions. The hospital discharge data provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

For Iowa, we developed a linked dataset between birth certificates and the Surveillance, Epidemiology, and End Results (SEER) cancer registry data. The cancer registry created the cancer incidence database based on the criteria: female cases 0 to 44 years at diagnosis, currently over 18 and diagnosed with cancer between 1973 and 2018. Cancer cases obtained from the state cancer registry were linked to birth certificate data to capture the birth of infants born to women with a prior cancer diagnosis. After matching the case dataset with the birth certificate files, two randomly selected control infants were selected that matched

the birth month and year of each case infant. To be eligible for selection, an infant in the control group required an Iowa resident mother who was 18 years of age or older at birth.

Study Population

We included live births of singletons or multiple gestation between 20- and 44-weeks. In California, we included live births from 2007–2012 and in Iowa, from 1989–2018. Women ≥45 years of age, with chronic hypertension or with a cancer type other than leukemia or lymphoma or more than one type of cancer were excluded. Women with chronic hypertension were excluded because we did not have diagnosis date that would ensure diagnosis of chronic hypertension occurred after cancer diagnosis. Only the first pregnancy within the cohort period was included for analysis.

Study Variables

The primary exposure was leukemia and lymphoma. In California, we used ICD-9 codes 201.x-202.x, 203.1x, 204.x-208.x, V10.6, and V10.7. For Iowa, we used the 3rd edition of the *International Classification of Diseases for Oncology*. Specifically, these are C024, C098-C099, C111, C142, C379, C422, C770-C779, C420, C421, and C424.

The primary outcome was hypertensive disorders of pregnancy defined as having new onset of hypertension during pregnancy that included gestational hypertension, preeclampsia or eclampsia. In California, the variables gestational hypertension, preeclampsia, and eclampsia were obtained from both birth certificates and the hospital discharge diagnoses (ICD-9 642.3, 642.4, 642.5, and 642.6). In Iowa, gestational hypertension and eclampsia information were obtained from birth certificates. There is no preeclampsia information in birth certificates in Iowa.

The covariates assessed include age, race (non-Hispanic White, Asian, Black, Hispanic, Other race), education (<12 years, 12 years, >12 years), smoking history during pregnancy (yes/no), prior live births (0, 1, 2, 3 or more), and plurality (singleton, twins or more). Prior live births are those pregnancies occurring outside our cohort time period. For those in the leukemia/lymphoma group, these could also be pregnancies that occurred prior to diagnosis. Overall, there was <5% missing from any one variable, except for prior live births, there was <13% missing in Iowa. All covariates for both California and Iowa were collected from birth certificate data. Additionally, in Iowa we assessed cancer characteristics using the SEER registry; in California we did not have cancer related characteristics. In Iowa, we evaluated cancer stage (local, regional, distant, unstaged), age at diagnosis, cancer treatment (chemotherapy only, chemotherapy with radiation, chemotherapy with surgery, chemotherapy with surgery and radiation, radiation only, radiation with surgery, surgery only, none), hormone therapy (yes/no), immunotherapy (yes/no), chemotherapy (yes/no), radiation (yes/no), and time from diagnosis to delivery (<3 years, 3–5 years, 6–8 years, and 9 or more years).

Statistical Analysis

Univariate and multivariate analysis were conducted using SAS 9.4 (SAS Institute, Cary, NC). We compared study characteristics based on cancer exposure using chi-square tests for

categorical variables and t-tests for continuous variables. For California, we used a logistic regression model to evaluate associations between hypertensive disorders of pregnancy and cancer. To account for matching in the Iowa data, we used a conditional logistic regression model for assessing the relationship between hypertensive disorders of pregnancy and cancer. Multivariable logistic regression models were used to adjust for potential confounders, which included age, race, education, smoking history during pregnancy, and plurality. A p-value <0.05 defined statistical significance.

Furthermore, we explored the potential impact of cancer therapies and evaluated the relationship between cancer treatments and prevalence of hypertensive disorders of pregnancy among leukemia/lymphoma patients in Iowa. We also conducted a sensitivity analysis to assess the risk of severe cases of hypertension in pregnancy among those with a history of leukemia/lymphoma in California by including only those with preeclampsia and eclampsia.

For California, methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California. De-identified data was provided to the researchers by the California Office of Statewide Health Planning and Development (Protocol # 12–09–0702) and determined not to qualify as human subjects research by the University of Iowa Institutional Review Board (IRB no.: 201602793). For Iowa, the study was approved by the University of Iowa Institutional Review Board. Data was approved for linkage by the Iowa Department of Public Health (RA 3873) and by the University of Iowa Institutional Review Board (IRB no: 201811805).

RESULTS

The lifetime prevalence of leukemia and lymphoma in both California and Iowa populations were very similar with 0.041% in California and 0.046% in Iowa. In California, a total of 2,469,649 women met our cohort criteria: a total of 1,024 women with diagnosis of leukemia/lymphoma and 2,468,625 women without any recorded cancer diagnosis. Among the women with leukemia/lymphoma, about 56.7% were identified through use of ‘V’ history codes. In the Iowa cohort, a total of 1,529 women, 515 having leukemia/lymphoma and 1,014 of their matched controls, met the cohort criteria.

The descriptive characteristics of both California and Iowa are shown in Table 1. The mean age at delivery was 28.1 years in California and 27.8 years in Iowa. Among women in California with leukemia/lymphoma, 43.6% were non-Hispanic White; in Iowa, 94.2% of the leukemia/lymphoma group were non-Hispanic White. In California, 50.6% controls were Hispanic; in Iowa, 85.8% of controls were non-Hispanic White. Compared with California mothers, Iowa mothers were more likely to be recorded as smoking during pregnancy (14.1% vs. 4.4%) and were more likely to have education beyond high school (66.3% vs. 45.1%). Overall, when compared to women without history of cancer, women in California and Iowa with history of leukemia/lymphoma were older at birth, more likely to be non-Hispanic White race/ethnicity, have more years of education, and less likely to have had a prior birth.

Cancer and treatment characteristics from the SEER registry in the Iowa cohort are displayed in Table 2. While leukemias are inherently widespread, SEER still applies staging and all leukemias are classified as distant. Most of the lymphoma patients in our Iowa cohort had regional cancer stage. All but 11% of women were diagnosed before 30 years of age. The time from cancer diagnosis to time of birth was nine or more years for 43.7% of women with leukemia/lymphoma history, with one-fifth of women having been diagnosed within the past three years. When assessing cancer treatment, about 49% were treated with only chemotherapy and 34.2% were treated with both chemotherapy and radiation, most being lymphoma patients. The majority of leukemia/lymphoma patients did not have any immunotherapies (95.9%).

The unadjusted and adjusted logistic regression models for California and Iowa are shown in Table 3. In California, prevalence of hypertensive disorders of pregnancy in the leukemia/lymphoma group was 7.1% and 5.8% in the non-cancer group. The corresponding prevalence in Iowa were 6.6% and 4.2%. The unadjusted odds ratio in California was 1.24 (95% CI 0.98–1.58) and 1.65 (95% CI 1.02–2.66) in Iowa. In California, history of leukemia/lymphoma was not significantly associated with risk of having hypertensive disorders of pregnancy compared to women without a history of cancer after adjusting for maternal age, race, education, plurality, and smoking (OR = 1.12; 95% CI 0.87–1.43). In Iowa, women with history of leukemia/lymphoma were at increased risk of hypertensive disorders of pregnancy compared to women without history of cancer after adjusting for age, race, plurality, and smoking (OR 1.86; 95% CI 1.07–3.23). This 12% and 86% increase in odds corresponds to a difference in risk of 0.8% between births with and without a history of leukemia/lymphoma in California and a difference of 2.2% in Iowa.

In Iowa analyses exploring relationship to cancer treatments (Table 4), after adjusting for cancer stage, diagnosis age, and time since diagnosis to delivery, there were no significant differences in the odds of hypertensive disorders of pregnancy by cancer treatment.

Additionally, in our sensitivity analysis in Table 5 evaluating the risk of preeclampsia and eclampsia among those with a history of leukemia/lymphoma in California, the unadjusted odds ratio was 1.40 (95% CI 1.05–1.86) and after adjusting for age, race, education, plurality and smoking, the odds ratio was 1.29 (95% CI 0.96–1.74).

DISCUSSION

In two different populations within the US, women with a history of leukemia/lymphoma were more likely to develop hypertensive disorders of pregnancy than women without this history, albeit with different strengths of association (California: OR = 1.12 (95% CI 0.87–1.43); Iowa: OR = 1.86 (95% CI 1.07–3.23)). In Iowa, the SEER registry data allowed further description of cancer characteristics: 89% of women with leukemia/lymphoma were diagnosed before 30 years of age, 43.7% were 9 or more years from the time of diagnosis to delivery, 83% had undergone chemotherapy and 47% radiation treatment.

There were differences between the two populations in demographic characteristics that could have led to the effect estimate differences; about half of the Californian cohort was

Hispanic and had no prior live births. However, in Iowa, more than 85% of the cohort was non-Hispanic White, and the majority had one or more prior live births. The differences in demographic characteristics such as prior live births are potentially due to Iowa having a stagnant population, as demonstrated in data going back to 1989 for births and cancer diagnosis from 1975 onward. These data suggest people in Iowa diagnosed with cancer stay within the state to have a baby years later and those not diagnosed with cancer also stay within Iowa for an extended time. Thus, we capture more data in Iowa about patient characteristics. In California, birth data were only available from 2007 to 2012, so information on prior live births is incomplete. Additionally, Iowa is comprised of a more rural population and California both rural and urban populations could also possibly explain differences in population characteristics.

The effect estimate differences between the two populations of Iowa and California could be due to the different ascertainment of the exposure of leukemia/lymphoma. In California, ICD-9 codes from hospital discharges were used to assess leukemia/lymphoma, whereas, cancer registry data was used in Iowa. The use of ICD-9 codes as opposed to verified cancer registry data could have led to misclassification of cancer history. There are yet to be any validation studies assessing ICD-9 diagnosis codes obtained from pregnancy hospital discharge data with registry data, which results in difficulty assessing the accuracy of cases in our population and led to potentially biased results.

Differences in outcome definition in California vs. Iowa may also contribute to the difference in effect estimates. We were able to combine data from both birth certificates and hospital discharges for gestational hypertension and pregnancy-induced hypertension in California (23, 24). Gestational hypertension is underreported in birth certificates (25–28). Including hospital information may have resulted in increased sensitivity but potentially at the cost of lower specificity compared with the Iowa case definition. However, in California, when we evaluated the severe cases of hypertension in pregnancy only (preeclampsia and eclampsia), the effect estimate increased. A more stringent definition for gestational hypertension led to larger effect estimate which, though not significant statistically, indicates consistency with the Iowa finding. Data collected in Iowa on our outcome of hypertensive disorders of pregnancy occurred over decades, when there were changes in collection of gestational hypertension information on birth certificates and modifications in diagnosis and treatment protocols for gestational hypertension. These are potential reasons for differences we see in the results between California and Iowa.

Our results are comparable to other existing studies. Haggar et al. conducted a study in Western Australia that found a 1.44 (95% CI 1.13–1.87) increased relative risk of preeclampsia among AYA cancer patients compared to those without history of cancer after adjusting for aboriginal status, previous cesarean section, maternal smoking, use of fertility treatment, residential remoteness, and hospital status (21). Even though that study included all cancers and only preeclampsia whereas we included only leukemia/lymphoma history and gestational hypertension and eclampsia in addition to preeclampsia, this result is very similar to our study, having a 1.2- and 1.9-times risk for gestational hypertension after adjusting for confounders. Another study found that that among those with Wilm’s

tumor, there was a threefold increased risk of gestational hypertension (RR = 3.29; 95% CI 2.29–4.71) (22).

Our study has potential limitations. Within the California data, we primarily used ICD-9 codes including V10 history codes to find our leukemia or lymphoma cases. This could have led to misclassification of the leukemia and lymphoma cases. Additionally, in California, we may have included some cancers that were diagnosed during rather than before pregnancy since we do not have cancer diagnosis dates. In our California cohort, ICD-9 diagnoses could have included some misclassified chronic hypertension in the outcome definition. However, we excluded women with chronic hypertension, increasing the likelihood that hypertension codes during pregnancy was gestational hypertension and not chronic hypertension. We also were not able to assess body mass index, an important risk factor for hypertension, due to high missingness of this variable in both Iowa and California. Another limitation of this study includes we did not have cancer treatment data for California. However, we were able to obtain treatment data for Iowa from the cancer registry to explore.

Despite these limitations, our study had several strengths. First, we had a large sample size with a diverse population. We included two very different populations: Iowa and California. Data from California includes a racially and ethnically diverse population, and data from Iowa contains rural and urban populations. Another strength of this study is the SEER registry cancer data in Iowa, providing verified information on cancer diagnoses, dates of diagnoses, and treatment. Furthermore, this is the first study to our knowledge addressing the relationship between leukemia/lymphoma with gestational hypertension and specifically looking at hypertension during pregnancy that includes gestational hypertension, preeclampsia, and eclampsia.

In conclusion, our results show increased risk for hypertensive disorders of pregnancy among women with history of leukemia or lymphoma. The strength of association was greatest and only statistically significant in the state of Iowa. While the effect for California was not statistically significant, sensitivity analysis with a more specific outcome definition resulted in a larger, though still nonsignificant, odds ratio. Different relationship magnitudes between these states may reflect chance variation, differences in data sources, or true differences in these relationships due to differences in prevalence of modifying factors such as body mass index or social determinants. Additional large-scale studies should be conducted that include verified cancer data to evaluate the relationship between leukemia/lymphoma and gestational hypertension. Overall, our study strengthens existing epidemiologic evidence of the relationship between history of leukemia/lymphoma with hypertensive disorders of pregnancy. Understanding complications of past cancer diagnoses and treatment on future pregnancies will help improve vigilance and healthcare resources from preconception through birth.

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Reference:

1. Keegan TH, Ries LA, Barr RD, Geiger AM, Dahlke DV, Pollock BH, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer 2016;122(7):1009–16. [PubMed: 26848927]
2. SEER NCI. Fast Stats 2018 [Available from: https://seer.cancer.gov/statfacts/.
3. Zebrack B, Bleyer A, Albritton K, Medearis S, Tang J. Assessing the health care needs of adolescent and young adult cancer patients and survivors. Cancer 2006;107(12):2915–23. [PubMed: 17103383]
4. Benedict C, Shuk E, Ford JS. Fertility Issues in Adolescent and Young Adult Cancer Survivors. Journal of adolescent and young adult oncology 2016;5(1):48–57. [PubMed: 26812452]
5. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012;118(6):1710–7. [PubMed: 21887678]
6. Schover LR. Patient attitudes toward fertility preservation. Pediatric blood & cancer 2009;53(2):281–4. [PubMed: 19301387]
7. Hudson MM. Reproductive outcomes for survivors of childhood cancer. Obstetrics and gynecology 2010;116(5):1171–83. [PubMed: 20966703]
8. Edgar AB, Wallace WH. Pregnancy in women who had cancer in childhood. European journal of cancer (Oxford, England : 1990) 2007;43(13):1890–4.
9. Emily G, Alka P, Jane M, Denise W. Reproductive health in female survivors of childhood cancer. The Obstetrician & Gynaecologist 2016;18(4):315–22.
10. Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. British journal of obstetrics and gynaecology 1999;106(12):1265–72. [PubMed: 10609720]
11. Green DM, Sklar CA, Boice JD Jr., Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27(14):2374–81. [PubMed: 19364956]
12. Spunt SL, Sweeney TA, Hudson MM, Billups CA, Krasin MJ, Hester AL. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23(28):7143–51. [PubMed: 16192598]
13. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. Human reproduction update 2009;15(3):323–39. [PubMed: 19174449]
14. Anderson C, Engel SM, Mersereau JE, Black KZ, Wood WA, Anders CK, et al. Birth Outcomes Among Adolescent and Young Adult Cancer Survivors. JAMA oncology 2017;3(8):1078–84. [PubMed: 28334337]
15. Lawrenz B, Henes M, Neunhoeffer E, Fehm T, Huebner S, Kanz L, et al. Pregnancy after successful cancer treatment: what needs to be considered? Onkologie 2012;35(3):128–32. [PubMed: 22414979]
16. Kasum M, Beketić-Orešković L, Peddi PF, Orešković S, Johnson RH. Fertility after breast cancer treatment. European Journal of Obstetrics and Gynecology and Reproductive Biology 2014;173:13–8. [PubMed: 24315568]
17. Cardous-Ubbink MC, Geenen MM, Schade KJ, Heinen RC, Caron HN, Kremer LC, et al. Hypertension in long-term survivors of childhood cancer: a nested case-control study. European journal of cancer (Oxford, England : 1990) 2010;46(4):782–90.
18. Barry E, Alvarez JA, Scully RE, Miller TL, Lipshultz SE. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert opinion on pharmacotherapy 2007;8(8):1039–58. [PubMed: 17516870]

19. Lipshultz SE, Adams MJ. Cardiotoxicity after childhood cancer: beginning with the end in mind. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28(8):1276–81. [PubMed: 20142585]

20. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation 2013;128(17):1927–95. [PubMed: 24081971]

21. Haggar FA, Pereira G, Preen D, Holman CDA, Einarsdottir K. Adverse Obstetric and Perinatal Outcomes following Treatment of Adolescent and Young Adult Cancer: A Population-Based Cohort Study. PloS one 2014;9(12):e113292. [PubMed: 25485774]

22. Reulen RC, Bright CJ, Winter DL, Fidler MM, Wong K, Guha J, et al. Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. Journal of the National Cancer Institute 2017;109(11).

23. Haghighat N, Hu M, Laurent O, Chung J, Nguyen P, Wu J. Comparison of birth certificates and hospital-based birth data on pregnancy complications in Los Angeles and Orange County, California. BMC pregnancy and childbirth 2016;16(1):93. [PubMed: 27121857]

24. Lydon-Rochelle MT, Holt VL, Cardenas V, Nelson JC, Easterling TR, Gardella C, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. American journal of obstetrics and gynecology 2005;193(1):125–34. [PubMed: 16021070]

25. Dietz P, Bombard J, Mulready-Ward C, Gauthier J, Sackoff J, Brozicevic P, et al. Validation of selected items on the 2003 U.S. standard certificate of live birth: New York City and Vermont. Public health reports (Washington, DC : 1974) 2015;130(1):60–70.

26. Gregory ECW MJ, Argov EL, Osterman MJK. Assessing the quality of medical and health data from the 2003 birth certificate revision: Results from New York City. National Vital Statistics Reports 2019;68(8):1–20.

27. Reichman NE, Schwartz-Soicher O. Accuracy of birth certificate data by risk factors and outcomes: analysis of data from New Jersey. American Journal of Obstetrics & Gynecology 2007;197(1):32.e1–.e8. [PubMed: 17618747]

28. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. Hypertension in pregnancy 2008;27(3):285–97. [PubMed: 18696357]

Highlights

- Risk of hypertensive disorders of pregnancy among women with history of leukemia/lymphoma
- No conclusive results for of hypertensive disorders of pregnancy by cancer treatments
- Higher risk of severe preeclampsia in women with a history of leukemia/lymphoma

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Table 1:

Descriptive characteristics by history of leukemia or lymphoma of California women who gave birth between 2007–2012 and Iowa women who gave birth between 1989–2018

		CALIFORNIA			IOWA		
Variable*	**Description**	**Total (N=2,469,649)**	**Leukemia/ Lymphoma+ (N=1024)**	**No Cancer (N=2,468,625)**	**Total (N=1529)**	**Leukemia/ Lymphoma+ (N=515)**	**No Cancer (N=1014)**
Hypertensive disorders of pregnancy	Gestational HTN, preeclampsia or eclampsia	143720 (5.8%)	73 (7.1%)	143647 (5.8%)	77 (5.0%)	34 (6.6%)	43 (4.2%)
	No hypertension	2325929 (94.2%)	951 (92.9%)	2324978 (94.2%)	1452 (95.0%)	481 (93.4%)	971 (95.8%)
Maternal Age At Delivery	<20	245360 (9.9%)	75 (7.3%)	245285 (9.9%)	92 (6.0%)	34 (6.6%)	58 (5.7%)
	20–24	530999 (21.5%)	177 (17.3%)	530822 (21.5%)	361 (23.6%)	92 (17.9%)	269 (26.5%)
	25–29	659507 (26.7%)	262 (25.6%)	659245 (26.7%)	506 (33.1%)	167 (32.4%)	339 (33.4%)
	30–34	608744 (24.6%)	281 (27.4%)	608463 (24.6%)	401 (26.2%)	157 (30.5%)	244 (24.1%)
	35–39	340692 (13.8%)	178 (17.4%)	340514 (13.8%)	139 (9.1%)	52 (10.1%)	87 (8.6%)
	40–44	84347 (3.4%)	51 (5.0%)	84296 (3.4%)	30 (2.0%)	13 (2.5%)	17 (1.7%)
Maternal Age (Continuous)	Mean and Std~	28.1 (6.3)	29.2 (6.2)	28.1 (6.3)	27.8 (5.4)	28.3 (5.4)	27.5 (5.3)
	Median and IQR~	28.0 (23.0, 33.0)	29.0 (25.0, 34.0)	28.0 (23.0, 33.0)	28.0 (24.0, 32.0)	28.0 (25.0, 32.0)	27.0 (23.0, 31.0)
	Min and Max~	(13.0, 44.0)	(13.0, 44.0)	(13.0, 44.0)	(16.0, 43.0)	(16.0, 43.0)	(18.0, 43.0)
Maternal Race/Ethnicity^	Asian	304811 (12.3%)	75 (7.3%)	304736 (12.3%)	^	^	^
	Black	124112 (5.0%)	53 (5.2%)	124059 (5.0%)	56 (3.7%)	13 (2.5%)	43 (4.2%)
	Hispanic	1249865 (50.6%)	353 (34.5%)	1249512 (50.6%)	70 (4.6%)	9 (1.8%)	61 (6.0%)
	Other race	179609 (7.3%)	97 (9.5%)	179512 (7.3%)	48 (3.1%)	8 (1.6%)	40 (3.9%)
	Non-Hispanic White	611252 (24.8%)	446 (43.6%)	610806 (24.7%)	1355 (88.6%)	485 (94.2%)	870 (85.8%)
Smoking History During Pregnancy	No smoking	2360594 (95.6%)	963 (94.0%)	2359631 (95.6%)	1302 (85.2%)	455 (88.3%)	847 (83.5%)

		CALIFORNIA			IOWA		
Variable*	**Description**	**Total (N=2,469,649)**	**Leukemia/ Lymphoma+ (N=1024)**	**No Cancer (N=2,468,625)**	**Total (N=1529)**	**Leukemia/ Lymphoma+ (N=515)**	**No Cancer (N=1014)**
	Smoked during pregnancy	109055 (4.4%)	61 (6.0%)	108994 (4.4%)	215 (14.1%)	55 (10.7%)	160 (15.8%)
Prior Live Births	0	1157853 (46.9%)	555 (54.2%)	1157298 (46.9%)	434 (28.4%)	195 (37.9%)	239 (23.6%)
	1	669706 (27.1%)	267 (26.1%)	669439 (27.1%)	496 (32.4%)	155 (30.1%)	341 (33.6%)
	2	382400 (15.5%)	123 (12.0%)	382277 (15.5%)	257 (16.8%)	60 (11.7%)	197 (19.4%)
	3 or more	258159 (10.5%)	79 (7.7%)	258080 (10.5%)	154 (10.1%)	32 (6.2%)	122 (12.0%)
Maternal Education	<12 years	636044 (25.8%)	135 (13.2%)	635909 (25.8%)	134 (8.88%)	29 (5.6%)	105 (10.4%)
	12 years	625588 (25.3%)	215 (21.0%)	625373 (25.3%)	370 (24.2%)	101 (19.6%)	269 (26.5%)
	>12 years	1113706 (45.1%)	628 (61.3%)	1113078 (45.1%)	1014 (66.3%)	383 (74.4%)	631 (62.2%)
Plurality	Singleton	2425843 (98.2%)	988 (96.5%)	2424855 (98.2%)	1484 (97.1%)	504 (97.9%)	980 (96.6%)
	Twins and more	43806 (1.8%)	36 (3.5%)	43770 (1.8%)	45 (2.9%)	11 (2.1%)	34 (3.4%)
Gestational Age of Delivery(in weeks)	Mean and Std~	38.7 (1.9)	38.3 (2.5)	38.7 (1.9)	38.9 (4.0)	38.6 (2.0)	39.0 (4.7)
Birth Weight (in grams)	Mean and Std~	3308.5 (549.8)	3233.5 (658.3)	3308.6 (549.7)	3398.2 (624.5)	3377.8 (584.6)	3408.6 (643.8)

*The data source for hypertensive disorders of pregnancy was from hospital discharge diagnoses for California and from birth certificate for Iowa.

All other variables from both states came from birth certificates.

+California: 324 Leukemia, 700 Lymphoma; Iowa: 126 Leukemia, 389 Lymphoma

^Maternal Race/Ethnicity: In Iowa, Asian was grouped with “Other race” due to <6 cell count

~Std: Standard deviation; IQR: Interquartile range; Min: Minimum; Max: Maximum

Table 2

: Cancer and treatment characteristics of Iowa study sample who were diagnosed between 1973–2018 by cancer type

Variable	Description	Data Source*	Leukemia (N=126)~	Lymphoma (N=389)~
Cancer Stage	Local	ICR		56 (14.4%)
	Regional			139 (35.7%)
	Distant		126 (100.0%)	80 (20.6%)
	Unstaged			114 (29.3%)
Age At Cancer Diagnosis	<5	ICR	37 (29.4%)	S
	5–9		36 (28.6%)	11 (2.8%)
	10–14		22 (17.5%)	36 (9.3%)
	15–19		11 (8.7%)	79 (20.3%)
	20–24		9 (7.1%)	129 (33.2%)
	25–29		7 (5.6%)	81 (20.8%)
	30–44		S	53 (13.6%)
Hormone Treatment	None	ICR	22 (17.5%)	239 (61.4%)
	Yes		104 (82.5%)	150 (38.6%)
Immune Treatment	None	ICR	118 (93.7%)	376 (96.7%)
	Yes		8 (6.3%)	13 (3.3%)
Time From Diagnosis To Delivery	<3 years	CALCULATED FROM ICR AND BC	12 (9.5%)	90 (23.1%)
	3–5 years		8 (6.3%)	99 (25.4%)
	6–8 years		7 (5.6%)	74 (19.0%)
	9+ years		99 (78.6%)	126 (32.4%)
Chemotherapy	No	ICR	S	86 (22.1%)
	Yes		123 (97.6%)	303 (77.9%)

Variable	Description	Data Source*	Leukemia (N=126)~	Lymphoma (N=389)~
Radiation Treatment	No	ICR	92 (73.0%)	182 (46.8%)
	Yes		34 (27.0%)	207 (53.2%)
Cancer Treatment Breakdown+	Chemotherapy only	GROUPED FROM ICR	89 (70.6%)	161 (41.4%)
	Both Chemotherapy and Radiation		34 (27.0%)	142 (36.5%)
	Radiation only		S	65 (16.7%)
	Neither Radiation nor Chemotherapy		S	21 (5.4%)

*Data source: ICR- Iowa Caner Registry

+A total of 93 women received surgery, typically coded as lymph node surgery

~S = suppressed cells (<6 cell count)

Table 3:

Risk of hypertensive disorders of pregnancy among women <45 years of age with leukemia/lymphoma who gave birth, by state

	California		Iowa[~]	
	N	**With hypertensive disorders of pregnancy (N (%))**	**N**	**With hypertensive disorders of pregnancy (N (%))**
Leukemia/Lymphoma, N (%)	1024	73 (7.1%)	515	34 (6.6%)
No Cancer, N (%)	2,468,625	143,647 (5.8%)	1014	43 (4.2%)
Unadjusted model (OR (95% Confidence Interval))		1.24 (0.98, 1.58)		1.65 (1.02, 2.66)[*]
Adjusted model (OR (95% Confidence Interval))[+]		1.12 (0.87, 1.43)		1.86 (1.07, 3.23)[*]

[*] $p<0.05$

[+] Adjusted for: age, race, education, plurality, smoking

[~] Uses conditional logistic regression modeling

Table 4:

Risk of hypertensive disorders of pregnancy among Iowa women <45 years of age with leukemia/lymphoma who gave birth between 1989–2018 based on cancer treatment

			Unadjusted model	Adjusted model*
Cancer Treatment+	**Total**	**With hypertensive disorders of pregnancy, N (%)~**	**OR (95 Confidence Interval (CI))**	**OR (95 Confidence Interval (CI))**
Chemotherapy only	250	14 (5.6%)	Ref	Ref
Both Chemotherapy and radiation	176	12 (6.8%)	1.23 (0.56, 2.74)	1.33 (0.57, 3.15)
Radiation only	65	6 (9.2%)	1.71 (0.63, 4.65)	1.98 (0.63, 6.22)
Neither Radiation nor Chemotherapy	24	S	1.53 (0.33, 7.18)	1.45 (0.29, 7.38)

*Adjusted for time from diagnosis to delivery, diagnosis age, and cancer stage

+A total of 93 women received surgery, typically coded as lymph node surgery

~S = Suppressed cells (<6 cell count)

Table 5:

Risk of preeclampsia and eclampsia among women <45 years of age with leukemia/lymphoma in California who gave birth

	Preeclampsia and Eclampsia only
Unadjusted model (OR (95% Confidence Interval))	1.40 (1.05, 1.86) *
Adjusted model (OR (95% Confidence Interval)) +	1.29 (0.96, 1.74)

* p<0.05

+ Adjusted for: age, race, education, plurality, smoking