Title

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Journal

Leukemia & Lymphoma, 59(2)

ISSN

1042-8194

Authors

Shliakhtsitsava, Ksenya
Romero, Sally AD
Dewald, Samantha Rose
et al.

Publication Date

2018-02-01

DOI

10.1080/10428194.2017.1352097

Peer reviewed

HHS Public Access

Author manuscript

Leuk Lymphoma. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Leuk Lymphoma. 2018 February ; 59(2): 381–397. doi:10.1080/10428194.2017.1352097.

Pregnancy and child health outcomes in pediatric and young adult leukemia and lymphoma survivors: a systematic review

Ksenya Shliakhtsitsava, MD,

Department of Pediatric Hematology & Oncology, University of California, San Diego, Address: UCSD Moores Cancer Center, 3855 Health Sciences Dr. #0901, La Jolla, CA, 92093-0901, Telephone: 858-822-7877

Sally A. D. Romero, PhD, MPH,

Department of Integrative Medicine, Memorial Sloan Kettering Cancer Center, Address: Bendheim Integrative Medicine Center, 1429 First Ave, New York, NY, 10021, Telephone: 646-888-0827

Samantha Rose Dewald, BS, and

School of Medicine, University of California, San Diego, Address: UCSD School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0606, Telephone: 586-219-1818

H. Irene Su, MD, MSCE

Department of Reproductive Medicine, Moores Cancer Center, University of California, San Diego, Address: UCSD Moores Cancer Center, 3855 Health Sciences Dr. #0901, La Jolla, CA, 92093-0901, Telephone: 858-822-5986

Abstract

As long-term survival is high for children and young adults diagnosed with leukemia and lymphoma, delineating maternal, fetal and offspring health risks is important to their family planning. This systematic review examined data comparing these health risks between leukemia and lymphoma survivors and women without a history of cancer. Following a search of Embase, PubMed, CINAHL, Cochrane and Web of Science, 142 articles were screened and 18 were included in this review. No higher risks of spontaneous abortion, maternal diabetes and anemia, stillbirth, birth defects, or childhood cancer in offspring were observed in survivors compared to controls. Important to counseling and clinical care, live birth rates were lower, while preterm birth and low birth weight risks were modestly higher in survivors compared to controls. Findings were largely reassuring but highlight the lack of data on maternal cardiopulmonary risks, differential risk by cancer treatment type, and interventions to decrease these risks.

Correspondence information: H. Irene Su, MD, MSCE, Address: UCSD Moores Cancer Center, 3855 Health Sciences Dr. #0901, La Jolla, CA, 92093-0901, Telephone: 858-822-5986, Facsimile: 858-246-0822, hisu@ucsd.edu.

Disclosure of Interest

The study complies with the current laws of the United States. The authors report no conflicts of interest.

Informed Consent

This study is exempt from institutional review board (IRB) review, and human consent is not required.

Keywords

leukemia; lymphoma; cancer survivorship; pregnancy; child health

Introduction

Advances in cancer treatment have enabled the majority of pediatric and young adult patients diagnosed with leukemia and lymphoma to become long-term survivors.[1] Following cancer treatment, these individuals frequently experience late effects, including reproductive health issues that require timely and appropriate diagnosis, treatment and follow-up.[2]

Many reproductive-aged women with a history of leukemia or lymphoma desire to have biological children[3] and are concerned that their cancer treatments may impact pregnancy and child health outcomes.[4, 5] To date, reproductive health studies have focused on infertility and ovarian failure, with less emphasis on the health of pregnancies that are achieved. While chemotherapy, radiation and surgery can adversely affect gametes, they may also impact the uterus and lead to co-morbidities that impact pregnancy. For example, radiation to the uterus has been shown to cause direct fibrosis, which can impair a woman's ability to carry a pregnancy to term.[6] In comparison, anthracycline chemotherapy is not known to directly affect the uterus, but resultant cardiomyopathy would increase maternal risks during pregnancy.

A number of cohort studies have examined the association between cancer treatments and maternal, fetal and child health outcomes in leukemia and lymphoma survivors. To support family building decision-making, we conducted a systematic review of maternal, fetal and child health outcomes for female pediatric and young adult survivors of leukemia and lymphoma.

Methods

Search strategy

This systematic review was conducted in accordance with standard PRISMA guidelines.[7] In June, 2017, the following databases were systematically searched: Embase (1980 to June 1, 2017), PubMed (1966 to June 1, 2017), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to June 1, 2017), COCHRANE (all years), and Web of Science (1900 to June 1, 2017). The bibliographies of all included studies were thoroughly screened for additional relevant references. Studies on female leukemia and lymphoma survivors with maternal and fetal pregnancy and child health outcomes were selected for full article review. Studies on fertility, males, non-humans, and other female cancer patients were excluded. Additionally, case reports and case series without controls were excluded. The final PubMed search strategy is detailed in the Supplementary Materials.

Outcome measures

The primary maternal outcomes were spontaneous abortions (SAB), pregnancy termination (TAB), maternal medical conditions during pregnancy and labor and delivery, i.e. gestational

diabetes, anemia, hypertension, pregnancy-induced hypertension, heart failure, uterine rupture, cesarean delivery, postpartum hemorrhage and death. The primary fetal and child health outcomes were live birth, stillbirth, preterm birth, low birth weight (LBW), small for gestational age (SGA), low Apgar scores, birth defects, sex ratio, childhood cancer risk and death.

Data collection

Two reviewers (IS, KS) independently screened the titles and abstracts of all citations against predefined inclusion and exclusion criteria. Discrepancies were discussed and resolved by consensus. Four authors (IS, SR, SD, KS) independently abstracted data on included articles. Abstracted data included study and participant characteristics, exposure and outcomes, and results. Risk of bias for all selected studies was independently evaluated by three review authors (IS, SR, KS) using the Cochrane risk assessment tool.[8] Specifically, confounding, selection bias and attrition were assessed. Each bias category was assigned a high, low or unclear risk. Consensus was reached to resolve discrepancies.

Results

The PRISMA flow diagram details study selection results (Figure 1).[7] Embase (n=67), PubMed (n=53), CINAHL (n=18), COCHRANE (n=16: n=1 clinical trial, n=15 reviews), and Web of Science (n=3) searches yielded 142 total articles. During the full text review, references were screened for potential eligible articles and 25 additional papers were identified and selected for full text screening. Duplicates were removed, leaving 132 articles for screening. Fifty-three articles were selected for full text review. Finally, a total of 18 studies were included in this review.

Included articles focused on maternal, fetal and child health outcomes in pediatric and young adult leukemia and lymphoma cancer survivors, compared to controls. Most studies used siblings without cancer and/or the general population as controls. Two studies used leukemia survivors as controls, compared to lymphoma survivors. All studies were retrospective cohorts in design. There were no articles excluded based on language. Given the heterogeneity of studies, we were unable to pool estimates for a meta-analysis or assign strength of recommendations based on the GRADE criteria.[9] Included studies described participants diagnosed and treated from the 1940s to early 2000s, but the majority of studies were of leukemia and lymphoma survivors treated from the 1970s to 1990s.

Maternal outcomes

Among maternal outcomes, studies reported data on SAB, TAB, and maternal co-morbidities during pregnancy and labor and delivery, including diabetes, hypertension during pregnancy, cesarean delivery, postpartum hemorrhage and anemia. No studies with specific data for leukemia and lymphoma survivors were found on heart failure, uterine rupture, and maternal death. The following results compare leukemia and lymphoma survivors to their siblings or the general population of women without cancer; data on pregnancies achieved via donated oocytes, and comparisons of leukemia to lymphoma survivors are presented separately.

Spontaneous abortion—Three studies reported SAB risks in childhood leukemia and lymphoma survivors (Table I).[10–13] All studies reported results from large survivorship cohorts including the Childhood Cancer Survivor Study (CCSS) from the United States,[10] Danish registry data,[12] and the German Childhood Cancer Registry.[13] Leukemia and/or lymphoma survivors were compared to either their nearest-age sibling without cancer[10, 12] or the general population.[12, 13] Pregnancy outcomes data were self-reported,[10, 13] or obtained from national healthcare registries.[12]

Absolute rates of SAB in leukemia and lymphoma survivors varied from 6–7% using a hospitalization registry[12] to 13–16% by self-report.[10, 13] In the CCSS, Danish registry data and German Childhood Cancer Registry, there was no increased rate of SAB in survivors compared to controls without cancer[10, 12–14] (Table II). However, in CCSS survivors of acute lymphoblastic leukemia (ALL) who exposed to cranial and spinal radiation, the relative risk (RR) of SAB was increased (RR 3.6, 95% CI 1.7–7.8) compared to ALL survivors who were not exposed to cranial and spinal radiation.[10] ALL participants with only cranial radiation did not have a higher rate of SAB (RR 1.6, 95% CI 0.8–3.0). There were no data comparing SAB rates by chemotherapy regimen in these studies.

Pregnancy termination—Three studies reported TAB rates for leukemia and lymphoma survivors (Table I).[10, 13, 15] These studies included the CCSS,[10] Danish registry data,[15] and the German Childhood Cancer Registry[13] and compared survivors to either siblings[10, 15] or a general population.[13, 15] TAB data were self-reported[10, 13] or obtained from national healthcare registries.[15]

Across studies, absolute rates of TAB in leukemia and lymphoma survivors varied from 7 to 22% (Table II). In the Danish data, there was no increased risk of TAB in survivors compared to controls without cancer.[15] Green et al reported an increased risk of TAB in leukemia survivors (RR 1.7, 95% CI 1.3–2.2) and HL survivors (RR 1.3, 95% CI 1.0–1.7) compared to sibling controls. The risk of TAB was not increased for non-Hodgkin's lymphoma survivors in CCSS.[10] The German Childhood Cancer Registry was the only study to report a higher TAB rate in the general population (17%) compared to leukemia survivors (7%).[13] There were no data comparing TAB rates by radiation or chemotherapy in these studies.

Maternal co-morbidities—Three studies reported results on gestational diabetes, anemia and cesarean delivery for leukemia and lymphoma survivors, deriving data from the U.S. SEER Registry,[16] North Carolina Cancer Registry,[17] and the Western Australian Cancer Registry,[18] (Table I). Survivors were compared to females without a history of cancer in all studies.[16–18]

There was no significantly increased risk for gestational diabetes[16, 18] or anemia[16] in survivors compared to controls (Table II). Two studies reported no increased risk of cesarean delivery,[16, 17] while Haggar et al reported an increased risk in leukemia survivors (adjusted RR 2.0, 95% CI 1.3–12.4) compared to females without a history of cancer.[18] In evaluating treatment exposures, Anderson et al reported no increased risk of cesarean delivery associated with radiation and/or chemotherapy exposure in lymphoma survivors.[17]

Maternal outcomes: lymphoma versus leukemia—Two additional studies compared maternal outcomes between lymphoma and leukemia survivors in the British Childhood Cancer Survivor Study (BCCSS) (Table I).[11, 19] One study included SAB and TAB risks[11], and the second study reported on cesarean delivery, hypertension during pregnancy, gestational diabetes, anemia, fetal malpresentation, and postpartum hemorrhage.[19] Pregnancy outcomes were self-reported[11] or obtained from hospitalization data.[19] Absolute rates of SAB were 17% in leukemia survivors, 14% among HL survivors, and 13% among NHL survivors.[11] No increased rates of SAB in lymphoma survivors compared to leukemia survivors were observed. Absolute rates of TAB were 13% in leukemia survivors and 12% among HL and NHL survivors.[11] No increased rates of TAB among lymphoma survivors compared to leukemia survivors were observed. There were no data comparing SAB rates by radiation or chemotherapy regimen.

Compared to leukemia survivors, lower rates of cesarean delivery were observed in HL survivors (elective cesarean delivery RR 0.6, 95% CI 0.3–1.1; emergency cesarean delivery RR 0.6, 95% CI 0.4–1.0), but not in NHL survivors.[19] Rates of gestational diabetes (2–4%) and anemia (6–7%) were similar among HL, NHL and leukemia survivors.[19] Hypertension during pregnancy occurred in 7% of HL survivors, 12% of NHL survivors and 9% of leukemia survivors, which were not significantly different.[19] Similarly, postpartum hemorrhage risks (9–12%) were also not increased in lymphoma survivors compared to leukemia survivors.[19]

Maternal outcomes following pregnancy using oocyte donation—One study reported pregnancy outcomes after pregnancy was achieved utilizing donor oocyte in a small cohort of leukemia and lymphoma survivors from a single fertility clinic in Spain (n=59) (Table I).[14] Medical record data of leukemia and lymphoma survivors who underwent oocyte donation were compared to those of females with no cancer history who underwent oocyte donation. Absolute rates of SAB in controls, leukemia survivors, NHL survivors and HL survivors were 30%, 55%, 7% and 16%, respectively (Table II).[14] Such a wide range of absolute risk was due in part to small numbers of survivors, but following Bonferroni correction, a history of leukemia and lymphoma was not associated with SAB.

Fetal and child health outcomes

The included studies reported live birth, stillbirth, preterm birth, LBW, SGA, low Apgar scores, need for resuscitation at the time of delivery, sex ratio, birth defects and chromosomal abnormalities, and childhood cancer risk. No studies with data on perinatal death in the offspring of leukemia and lymphoma survivors were found. Following results comparing leukemia and lymphoma survivors to their siblings or the general population of women without cancer, data on pregnancies achieved via donated oocytes and comparisons of leukemia to lymphoma survivors are presented separately.

Live birth—Two studies reported on rates of live birth in pregnant survivors and compared them to the general population [11] or siblings without a history of cancer[10] (Table I). Additionally, two studies reported low Apgar scores rates[17, 18], and one study reported need for neonatal resuscitation at the time of delivery.[18] These studies included the CCSS,[10]

BCCSS,[11] North Carolina Cancer Registry,[17] and Western Australian Cancer Registry.[18] Live birth outcomes data were self-reported.[10, 11] Information on neonatal resuscitation and Apgar scores was derived from linked registry data.[17, 18]

Among pregnancies in leukemia and lymphoma survivors, live birth rates were high, 62%, 66%, and 67% for leukemia, HL and NHL survivors, respectively (Table III). [10] Live birth rates were 70% for sibling controls.[10]

Overall, lower rates of live birth after a pregnancy was achieved were observed for leukemia and lymphoma survivors compared to controls (Table III). CCSS cohort data showed lower live birth rates in leukemia survivors (RR 0.6 [95% CI 0.5–0.8]), HL survivors (RR 0.8 [95% CI 0.7–0.9]) and NHL survivors (RR 0.8 [95% CI 0.6–1.1]) when compared to sibling controls.[10] Similarly, the number of live births observed from leukemia and lymphoma survivors was lower than expected in the general population (Observed/Expected [O/E] for leukemia 0.6 [95% CI 0.6–0.7]; O/E for HL 0.9 [95% CI 0.8–0.9]; O/E for NHL 0.8 [95% CI 0.7–0.9]).[11] Rates of low Apgar scores (<7) and need for neonatal resuscitation did not appear higher than controls (Table III).[17, 18] There were no data comparing live birth rates by radiation or chemotherapy in these studies.

Stillbirth—One study reported stillbirth outcomes from the CCSS cohort (Table I).[10] Survivors were compared to siblings without cancer and stillbirth outcomes were self-reported.

Absolute rates of stillbirths were very low (Table III). Stillbirth rates were 1.2% for leukemia survivors, 1.0% for HL survivors, and 1.3% in NHL survivors, these rates were not significantly different from the control population (0.7%).[10] There were no data comparing stillbirth rates by radiation or chemotherapy in the study.

Preterm birth—Five studies reported results on preterm birth prior to 37 weeks gestation for leukemia and lymphoma survivors (Table I).[16–18, 20, 21] These studies included the CCSS,[20] U.S. SEER Registry data,[16] North Carolina Cancer Registry data,[17] Western Australia Cancer Registry data,[18] and a single institution in the United Kingdom.[21] Preterm births were either self-reported[20, 21] or obtained from national healthcare registries.[16, 18] The general population or nearest-age sibling without cancer served as controls in all studies.[16–18, 20, 21]

In some studies, higher rates of preterm birth were observed in both leukemia and lymphoma survivors compared to controls (Table II). Mueller et al found an increased risk of preterm birth in leukemia (RR 2.6, 95% CI 1.8–3.6) and lymphoma survivors (RR 1.8, 95% CI 1.3–2.5) compared to controls.[16] Signorello et al reported an increased risk of preterm birth among survivors (19% for leukemia and HL survivors, 21% for NHL survivors) compared to controls (13%).[20] Anderson et al reported higher prevalence of preterm birth among HL (adjusted prevalence ratio [APR] 1.6, 95% CI 1.1–2.4) and NHL survivors (APR 2.1, 95% CI 1.4–3.1) compared to population controls.[17] Additionally, in the same study NHL survivors were more likely to have preterm birth at < 34 weeks gestation (APR 3.4, 95% CI 1.9–6.2) and this result remained significant after patients with history of radiation

were excluded from the analysis (APR 4.2, 95% CI 2.2–8.3).[17] Similarly after adjusting for confounding, Haggar et al reported an increased risk of preterm birth in leukemia survivors compared to controls (adjusted relative risk [ARR] 1.7, 95% CI 1.2–2.4), but not in lymphoma survivors.[18] In a small cohort of HL survivors at a single institution, 8.3% of HL survivors delivered preterm, compared to 7.1% of the general population (RR 0.9, 95% CI 0.3–2.5).[21] One study evaluated radiation and chemotherapy treatment effects on prematurity (Table III).[17] For HL patients, radiation alone seemed to increase prematurity risk (APR 6.0, 95% CI 3.1–11.6). However, when data was analyzed combining radiation and chemotherapy exposures, risk was no longer elevated (APR 1.0, 95% CI 0.5–2.2). For NHL patients, combining radiation and chemotherapy exposures led to an increased risk of prematurity (APR 2.6, 95% CI 1.2–5.9).[17]

Low birth weight and small for gestational age—Five studies reported LBW (< 2500 grams) outcomes in survivors, while two study also reported SGA outcomes (Table I).[16–18, 20, 21] These studies included the CCSS,[20] U.S. SEER Registry,[16] North Carolina Cancer Registry,[17] the Western Australian Cancer Registry,[18] and one additional single-center study from the United Kingdom.[21] In these studies, survivors were compared to siblings[20] without cancer or the general population[11, 16–18, 21]. LBW and SGA outcomes were ascertained by self-report,[20, 21] registry data[18] or birth certificate data.[16, 17]

Absolute rates of LBW neonates varied between 9 to 10% for leukemia survivors, 6 to 10% for HL survivors, and 10 to 19% for NHL survivors (Table III). Consistent with higher rates of preterm deliveries, more LBW neonates were observed in survivors compared to controls. For leukemia survivors, the relative risk was increased almost 1.5 fold using cases from the SEER registry (RR 1.5, 95% CI 1.0–2.1);[16] the adjusted relative risk compared to controls was 1.8 times higher in the Western Australian registry (95% CI 1.4–2.6).[18] For lymphoma survivors, the adjusted prevalence ratio of LBW neonates was 1.4 times higher (95% CI 0.9–2.3) for HL survivors and 2.4 times higher for NHL survivors (95% CI 1.6–3.7) compared to women without cancer.[17] Of note, the CCSS and North Carolina Cancer registry data showed no higher rates of SGA in leukemia survivors compared to controls (Table III).[17, 20]

Additionally, in the small cohort of 26 HL survivors, a slightly higher proportion of LBW infants in survivors was observed (10.6% offspring of survivors vs 6.7% offspring of controls). This difference was not statistically significant.[21] In two studies on SGA, HL and NHL were not associated with this outcome.[17, 20] One study reported LBW and SGA rates by radiation or chemotherapy.[17] For HL survivors, any radiation therapy alone was associated with increased LBW births compared to the general population (APR 4.6, 95% CI 1.9–11.1). For survivors exposed to both radiation and chemotherapy, LBW risk was no longer increased. For NHL survivors, chemotherapy alone was associated with LBW risk (APR 3.3, 95% CI 2.1–5.3), while the combination of radiation and chemotherapy exposures (was not (APR 1.8, 95% CI 0.5–7.1).[17] Treatment exposures were not associated with SGA.

Sex ratios and birth defects—Four studies evaluated risk of birth defects and altered sex ratios in offspring of leukemia and lymphoma survivors (Table I).[21–24] Birth defects included malformations, deformations, and chromosomal anomalies. These studies were from Denmark (Danish registry data),[24] the United Kingdom (National Registry of

Childhood Tumors cohort and a small single-center cohort of HL patients),[21, 22] and the United States (Children's Cancer Group).[23] Data were ascertained by self-report[21, 23], health practitioner report,[22] or from registries.[24] For two studies, offspring of male and female survivors were reported together.[22, 23]

No alteration in offspring male to female sex ratio was noted in survivors compared to controls,[21–24] and no increased risk of birth defects was observed[22, 23] (Table III). Among survivors, several exposures were tested for their association with sex ratio. Higher cyclophosphamide exposure (>1 g/m^2), anthracycline exposure, and radiation were not statistically significantly associated with altered sex ratio.[23] Similarly, Winther et al showed that radiation was not associated with altered offspring sex ratio.[24]

Childhood cancer risk—Three studies evaluated childhood cancer risk in offspring of survivors (Table I).[22, 25, 26] These studies linked pregnant women with their offspring and identified leukemia and lymphoma survivors versus controls using data from cancer registries of Denmark, Finland, Iceland, Norway, Sweden, or the United Kingdom. Leukemia and lymphoma survivors were compared to siblings without cancer or the general population. Registry data were used to ascertain the outcomes.

Sankila et al reported childhood cancer in 1.7% of offspring of leukemia survivors and 0.3% of offspring of NHL survivors; these incidence rates of childhood cancer in offspring were not higher in leukemia and NHL survivors compared to the general population.[25] This finding was consistent with the other studies[22, 26] (Table III).

Fetal and child health outcomes: lymphoma versus leukemia—Two additional studies compared fetal outcomes between lymphoma and leukemia survivors in BCCSS (Table I).[11, 19] One study included live births,[11] and both studies included information on stillbirth, preterm birth and LBW outcomes (Table III). Fetal and child health outcomes were self-reported[11] or obtained from inpatient hospitalization data.[19]

Among pregnant women, absolute rates of live birth were similar between leukemia and lymphoma survivors (70% vs 72–75% respectively).[11] Stillbirth rates ranged from 0 to 0.9%; HL and NHL survivors did not have higher risk of stillbirth compared to leukemia survivors.[11] Compared to leukemia survivors, no increased risk of preterm birth was observed among HL and NHL survivors.[11, 19] Relative to controls, HL survivors did not have higher rates of LBW (Table III).[11, 19] The Odds of LBW was increased 2.1 fold for NHL survivors (95% CI 1.0–4.8) compared to leukemia survivors.[11] There were no data comparing fetal and child health outcomes by radiation or chemotherapy in these studies.

Fetal and child health outcomes of pregnancies resulting from oocyte donation—Outcomes after pregnancy was achieved by utilizing donor oocyte were reported in two small cohorts of leukemia and lymphoma survivors from fertility clinics in Spain.[14, 27] In these studies, medical records of leukemia and lymphoma survivors who underwent oocyte donation were compared to those of females with no cancer history who also underwent oocyte donation.

In women undergoing fertility treatment using donated oocytes, live birth rates per embryo transfer ranged from 20% in 15 leukemia survivors to 50–54% in 44 lymphoma survivors to 39% in 17844 controls.[14] Leukemia survivors had lower live birth rates per embryo transfer than both controls and survivors of HL and NHL.[14] Once pregnant, live birth rates were similarly high in leukemia survivors (80%), lymphoma survivors (71–100%) and controls (70%).[27]

Discussion

Since the majority of pediatric and young adult leukemia and lymphoma patients will become long-term survivors, assessing maternal, fetal and child health outcomes is important for counseling and caring for this population. This systematic review found a number of large cohort and registry studies from North America and Europe have compared these reproductive outcomes in leukemia and lymphoma survivors to those of controls without a history of cancer. Overall, no higher risks of SAB, maternal diabetes and anemia during pregnancy were observed for survivors compared to controls, while conflicting data have been reported on whether survivors have increased risks of TAB and cesarean delivery risk. Survivors are at higher risk of preterm birth and delivering low birth weight babies, but offspring of survivors appear to be at no higher risk of stillbirth, birth defects, or childhood cancer. Summarized in Table IV, these findings are largely reassuring, but highlight the lack of data on 1) whether specific leukemia and lymphoma treatments impart higher pregnancy and child health risks and 2) other maternal health risks, including cardiopulmonary complications, hypertension, preeclampsia, and post-partum hemorrhage.

Spontaneous abortion rates were higher only in a subgroup of leukemia survivors, acute lymphoblastic leukemia (ALL) survivors treated with cranial and spinal radiation treatment, consistent with data suggesting abdominal/pelvic radiation adversely impacts pregnancy outcomes.[10, 12] Following prior abdominal/pelvic radiation, SAB risk increased 1.5- to 2-fold in childhood cancer survivors, and SAB is hypothesized to be a result of direct radiation damage to endometrium leading to atrophy, fibrotic myometrium, and/or uterine vessels disruption.[28, 29] The effect of cranial radiation is less clear. While cranial radiation can disrupt hypothalamic-pituitary signaling, ALL survivors of the CCSS who received only cranial radiation alone did not have a higher SAB rate compared to controls. Moreover, among all CCSS participants, cranial and spinal radiation was associated with an increased second trimester SAB risk, not first trimester; physiologically, the placenta has assumed endocrine support of the pregnancy in the second trimester, with little contribution from hypothalamic-pituitary axis. It is possible that an increased SAB risk is related to scatter radiation involving pelvic organs in patients exposed to spinal radiation. Survivors need to be aware of increased SAB risk following cranial and spinal radiation.

Pregnancy termination in these populations show no higher rates than controls, but suggest that unintended pregnancies are occurring in this population. Concordant with these findings are recent studies showing lower rates of using highly effective methods of contraception in cancer survivors compared to the general population.[30, 31] In two cohorts, family planning counseling was associated with use of highly effective methods of contraception,

highlighting a potential intervention to help prevent unintended pregnancies and pregnancy terminations.[30, 31]

Limited studies evaluated maternal health risks during pregnancy, none on interventions to modify these risks. Akin to the general population of female childhood cancer survivors, leukemia and lymphoma survivors are at higher risk of cesarean delivery, but the reasons behind this increased rate are unknown.[18, 32] Importantly, childhood cancer survivors exposed to anthracyclines, especially in higher doses and/or chest radiation are at risk of developing cardiomyopathy.[33] The absolute risk of pregnancy-associated cardiomyopathy was low (0.3%) in female participants of the CCSS who have had a pregnancy, including 1 case among 317 leukemia survivors (0.3%).[33] But this risk may be 10-fold higher than the risk estimated in the general population of women (0.03%).[34] Replicative, adequately powered studies comparing peripartum cardiomyopathy risks between leukemia and lymphoma survivors and the general population are needed.

Following pregnancy, live birth rates were high, but lower in survivors compared to controls.[10] This is not explained by infertility, as participants who were not pregnant were not included in these denominators, but partially explained by modestly higher SAB and TAB rates. Moreover, preterm birth and LBW babies occurred 1.5- to 2-fold more frequently in leukemia and lymphoma survivors. Coupled to limited data reporting no increase in risk of SGA, these findings suggest that LBW occurred as part of preterm birth, but not as part of growth restriction. Beyond counseling survivors, more work is needed to elucidate if preterm births are iatrogenic or spontaneous and whether interventions, such as intramuscular progesterone for spontaneous preterm birth, could decrease risks in leukemia and lymphoma survivors.

Data on maternal and fetal outcomes following pregnancies achieved via oocyte donation to leukemia and lymphoma survivors were included and appeared similar to women without cancer undergoing oocyte donation. As fertility awareness increases in this population, more data on the outcomes of using autologous oocytes as well as longer-term child health outcomes are needed.

Several limitations should be discussed. Because of heterogeneity of outcomes, it was not possible to pool data for a meta-analysis to generate more precise risk estimates. In addition, the majority of studies included all childhood cancer survivors and did not generate additional treatment-based risks for outcomes within the leukemia and lymphoma population. For generalizability, the treatment era needs to be considered. The majority of studies in this review included survivors treated from the 1970s to 1990s. Temporal changes in treatments have included: 1) decreased radiation exposure; 2) increased surveillance of late effects; and 3) increased utilization of targeted therapy. While follow up, contemporary data are needed, these changes are anticipated to reduce reproductive health late effects.

This study provides summarized data on maternal, fetal and child health outcomes to facilitate reproductive health counseling for female leukemia and lymphoma survivors considering pregnancy.

Conclusion

For pediatric and young adult leukemia and lymphoma survivors, maternal, fetal and child health outcomes following cancer treatment are largely reassuring. Modest increases in risk of spontaneous abortions in some populations, preterm birth and low birth weight are important to consider in counseling and caring for this population. Currently, we have a dearth of data to support counseling on cardiovascular disease and uterine rupture in pregnancy; perinatal death; premature birth etiology; newer therapies effect on maternal and fetal health; and maternal, fetal and child health outcomes of assisted reproduction using autologous oocytes. Further, considerable gaps exist regarding research on sub-populations at the highest risks of adverse perinatal outcomes and interventions to modify these risks.

Acknowledgments

This study was supported in part by the Doris Howell Foundation Community Engagement Initiative, the California Breast Cancer Research Program Translational Award 200B-0 144, and NIH grant HD080952-03. The content is solely the responsibility of the authors and does not necessarily represent official views of the funding organizations.

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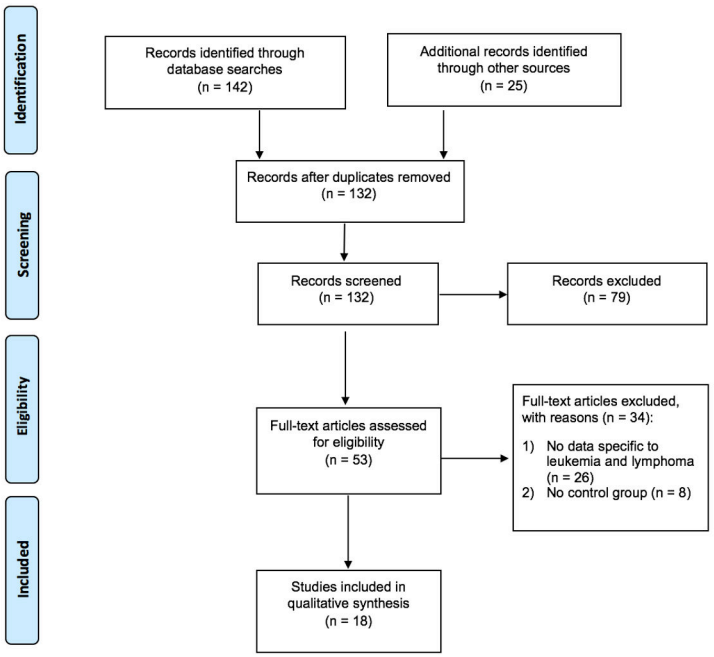

Figure 1.
PRISMA Flow Diagram

Table I

Summary of Studies

Reference	Study Design	Cancer survivors	Controls	Exposure	Outcome
Anderson et al, 2017[17]	Retrospective cohort Country: United States North Carolina Cancer Registry Registry linked to state birth certificate files	Lymphoma Age 15–39 at diagnosis Diagnosed 2000–2013 Live births 2000–2014 N=179 HL survivors with live, singleton births N=110 NHL survivors with live, singleton births	Matched births in women without cancer N=12990 women with live, singleton births	HL NHL Chemotherapy Radiation therapy	**Maternal:** • Cesarean delivery **Fetal/Child:** • Preterm birth (late preterm <37 weeks; early preterm <34) • LBW • SGA • Low Apgar score (<7)
Green et al, 2002[10]	Retrospective cohort Country: United States CCSS Self-reported pregnancy outcomes	Leukemia or lymphoma Diagnosed 1970–1986 Age <21 at diagnosis ≥5 years as survivors N=922 pregnancies in leukemia survivors N=1082 pregnancies in HL survivors N=300 pregnancies in NHL survivors N=178 pregnancies in ALL survivors	Nearest-age sibling without cancer N=1903 pregnancies in female siblings	Leukemia HL NHL Radiation therapy in ALL	**Maternal:** • SAB • TAB **Fetal/Child:** • Live birth • Stillbirth
Haggar et al, 2014[18]	Retrospective cohort Country: Australia Western Australian Cancer Registry linked to pregnancy and delivery outcome data	Leukemia or lymphoma Age 15–39 at diagnosis Diagnosed 1982–2007 N=57 leukemia survivors with pregnancy ≥20 weeks N=152 lymphoma survivors with pregnancy ≥20 weeks	Females with no cancer history		**Maternal:** • Gestational diabetes • Cesarean delivery **Fetal/Child:** • Preterm birth (<37 weeks) • LBW • Low Apgar score (<7) • Resuscitation
Hawkins et al, 1995[22]	Retrospective cohort Countries: England and Wales National Registry of Childhood Tumors General practitioner-reported outcomes	Leukemia or NHL Age <15 at diagnosis Diagnosed after 1940 N=382 births in 788 male and female leukemia and NHL survivors	General population of England	Leukemia NHL	**Fetal/Child:** • Birth defects • Offspring sex ratio • Childhood cancer

Reference	Study Design	Cancer survivors	Controls	Exposure	Outcome
Kenney et al, 1996[23]	Retrospective cohort Country: United States Children's Cancer Group Self-reported outcomes verified by medical record review	Leukemia Diagnosed 1970–1987 Treated <20 years of age ≥2 years as survivors Age ≥18 N=140 offspring in 93 male and female survivors	Female siblings without cancer N=409 controls N=228 offspring in 122 controls	Leukemia	**Fetal/Child:** • Birth defects • Offspring sex ratio
Madanat-Harjuoja et al, 2010[26]	Retrospective cohort Country: Finland Finnish Cancer Registry linked to offspring Excluded hereditary cancer syndromes	Leukemia or lymphoma Diagnosed 1953–2004 Age <35 at diagnosis Age ≥16 N=581 leukemia survivors with 1064 offspring N=1101 HL survivors with 2164 offspring N=686 NHL survivors with 1393 offspring	Female siblings without cancer	Leukemia NHL HL	**Fetal/Child:** • Childhood cancer
Mueller et al, 2009[16]	Retrospective cohort Country: Unites States SEER registry-identified cancer population linked to 4 states' birth records Birth certificate outcomes	Leukemia or lymphoma Diagnosed 1973–2000 Age <20 at diagnosis First live birth after cancer between 1973–2000 N=87 leukemia survivors with live births N=202 lymphoma survivors with live births	Matched births in women without cancer N=14278 women with live births	Leukemia Lymphoma	**Maternal:** • Gestational diabetes • Cesarean delivery • Anemia • Pre-eclampsia **Fetal/Child:** • Preterm birth (<37 weeks) • LBW
Munoz et al, 2015[14]	Retrospective cohort Country: Spain Fertility clinics Outcomes from medical records	Leukemia or lymphoma Cancer treatment 2000–2012 Pregnancy utilizing donor oocyte N=31 HL survivors (76 fertility treatment cycles) N=15 leukemia survivors (49 cycles) N=13 NHL survivors (24 cycles)	No cancer treatment Pregnancy utilizing donor oocyte N=17844 women (29778 cycles)	Leukemia HL NHL	**Maternal:** • SAB (<12 weeks) **Fetal/Child:** • Live birth
Reulen et al, 2009[11]	Retrospective cohort Countries: England and Wales BCCSS Self-reported pregnancy outcomes	Leukemia or lymphoma Diagnosed 1940–1991 ≥5 years as survivors Age ≥16 N=791 pregnancies in leukemia survivors N=346 pregnancies in HL survivors N=209 pregnancies in NHL survivors	Live birth: General population of England and Wales Other outcomes: Leukemia survivors as reference	Leukemia HL NHL Chemotherapy Radiation therapy	**Maternal:** • SAB (<24 weeks) • TAB **Fetal/Child:** • Live birth • Stillbirth • Preterm birth (<37 weeks) • LBW

Reference	Study Design	Cancer survivors	Controls	Exposure	Outcome
Reulen et al, 2017[19]	Retrospective cohort Countries: England BCCSS BCCSS cohort linked to inpatient hospitalizations for births	Leukemia or lymphoma Diagnosed 1940–1991 ≥5 years as survivors Age ≥16 N=915 births in 546 leukemia survivors N=153 births in 93 HL survivors N=111 births in 69 NHL survivors	Leukemia survivors as reference	Leukemia HL NHL	**Maternal:** • Cesarean delivery • Hypertension complicating pregnancy • Gestational diabetes • Anemia • Malpresentation • Postpartum hemorrhage **Fetal/Child:** • Stillbirth • Preterm birth (< 37 weeks) • LBW
Sankila et al, 1998[25]	Retrospective cohort Countries: Denmark, Finland, Iceland, Norway, Sweden Cancer registries Cancer population linked to their offspring	Leukemia or lymphoma Age <20 at diagnosis Age ≥15 Diagnosed 1943–1991 N=181 offspring in 136 leukemia male and female survivors N=924 offspring in 541 male and female lymphoma survivors	General populations of Denmark, Finland, Iceland, Norway, Sweden	Leukemia Lymphoma	**Fetal/Child:** • Cancer in offspring
Signorello et al, 2006[20]	Retrospective cohort Country: United States CCSS Self-reported pregnancy outcomes	Leukemia or lymphoma Diagnosed 1970–1986 Age <21 at diagnosis ≥5 years as survivors N=291 leukemia survivors with live births N=337 HL survivors with live births N=87 NHL survivors with live births	Nearest-age sibling without cancer N=1175 live births in 601 female siblings	Leukemia HL NHL	**Fetal/Child:** • Preterm birth (<37 weeks) • LBW • SGA
Swerdlow et al, 1996[21]	Retrospective cohort Country: England Single hospital Self-reported outcomes	HL Treated l between 1970–1991 Age <40 at diagnosis Age ≥18 N=49 live births in 44 male and female survivors	General population of England and Wales	HL	**Fetal/Child:** • Preterm birth (<37 weeks) • LBW • Offspring sex ratio
Vernaeve et al, 2007[27]	Retrospective cohort Country: Spain Single fertility clinic Outcomes from medical records	Leukemia or lymphoma Recipients of oocyte donation 2000–2005 History of chemotherapy and/or radiation therapy N=7 leukemia survivors with pregnancy N=12 HL survivors with pregnancy N=3 NHL survivors with pregnancy	N=33 recipients of oocyte donation with pregnancy	Leukemia HL NHL	**Fetal/Child:** • Live birth

Reference	Study Design	Cancer survivors	Controls	Exposure	Outcome
Winther et al, 2003[24]	Retrospective cohort Country: Denmark Danish Cancer Registry linked to birth, death, hospitalization and TAB registries	Leukemia or lymphoma Age <20 at diagnosis Diagnosed 1943–1996 Children born 1968–2000 N=78 births in 45 leukemia survivors N=139 births in 81 lymphoma survivors	N=1986351 births in the general population	Leukemia Lymphoma Radiation treatment	**Fetal/Child:** • Offspring sex ratio
Winther et al, 2008[12]	Retrospective cohort Country: Denmark Danish Cancer Registry linked to birth, death, hospitalization and TAB registries	Leukemia or lymphoma Diagnosed 1950–1996 Age <20 at diagnosis Age ≥15 N=158 pregnancies in 72 leukemia survivors N=205 pregnancies in 93 lymphoma survivors	N=5092 pregnancies in 1944 sibling controls N=27989 pregnancies in 11257 matched population controls	Leukemia Lymphoma	**Maternal:** • SAB
Winther et al, 2009[15]	Retrospective cohort Country: Denmark Danish Cancer Registry linked to birth, death, hospitalization and TAB registries	Leukemia or Lymphoma Diagnosed 1950–1996 Age <20 at diagnosis Age ≥15 N=72 leukemia survivors with pregnancy (158 pregnancies) N=93 lymphoma survivors with pregnancy (205 pregnancies)	Female sibling without cancer N=1944 sisters with pregnancy (5092 pregnancies)	Leukemia Lymphoma	**Maternal:** • TAB
Zynda et al, 2012[13]	Retrospective cohort Country: Germany German Childhood Cancer Registry Self-reported pregnancy outcomes	Leukemia Diagnosed 1980–2004 N=180 leukemia survivors with pregnancy	General population of Germany	Leukemia	**Maternal:** • SAB

ALL - Acute Lymphoblastic Leukemia, BCCSS - British Childhood Cancer Survivor Study, CCSS - Childhood Cancer Survivor Study, HL - Hodgkin's lymphoma, LBW - low birth weight (< 2500 grams), MR - medical records, NHL - non-Hodgkin's lymphoma, SAB - spontaneous abortion, SGA - small for gestational age, SEER - Surveillance, Epidemiology, and End Results Program, TAB - termination abortion, N/A - not applicable

Table II

Summary of Findings for Maternal Pregnancy Outcomes

Reference	SAB	TAB	Maternal co-morbidity
Anderson et al, 2017[17]	--	--	**Cesarean delivery** **Control** 33% **HL** 33%, APR 1.1 (95% CI 0.9–1.3) **HL radiation (no chemotherapy)** APR 1.5 (95% CI 0.7–3.2) **HL chemotherapy (no radiation)** APR 1.04 (95% CI 0.8–1.4) **HL radiation and chemotherapy** APR 1.1 (95% CI 0.8–1.5) **NHL** 42% APR 1.2 (95% CI 0.9–1.5) **NHL radiation (no chemotherapy)** APR 1.3 (95% CI 0.7–2.6) **NHL chemotherapy (no radiation)** APR 1.3 (95% CI 0.9–1.7) **NHL radiation and chemotherapy** APR 1.0 (95% CI 0.5–2.0)
Green et al, 2002[10]	**Control** 14.7% **Leukemia** 14.4%, RR 1.2 (95% CI 0.9–1.6) **HL** 14.8%, RR 1.1 (95% CI 0.9–1.4) **NHL** 16.3%, RR 1.2 (95% CI 0.8–1.7) **ALL No RT** 9.9% (control for RT) **ALL Cranial + spinal RT** 27.8%, RR 3.6 (95% CI 1.7–7.8) **ALL Cranial RT** 13.4%, RR 1.6 (95% CI 0.8–3.0)	**Control** 11.6% **Leukemia** 18.0%, RR 1.7 (95% CI 1.3–2.2) **HL** 15.2%, RR 1.3 (95% CI 1.0–1.7) **NHL** 14.7%, RR 1.2 (95% CI 0.8–1.2)	--
Haggar et al, 2014[18]	--	--	**Gestational diabetes** **Leukemia** ARR 1.2 (95% CI 0.2–9.4) **Lymphoma** ARR 1.5 (95% CI 0.8–2.8) **Cesarean delivery** **Leukemia** ARR 2.0 (95% CI 1.3–12.4) **Lymphoma** ARR 1.5 (95% CI 1.0–2.2)
Mueller et al, 2009[16]	--	--	**Gestational diabetes** **Control** 1.4% **Leukemia** RR 1.5 (95% CI 0.4–5.8) **Lymphoma** RR 0.4 (95% CI 0.06–3.0); **Maternal anemia** **Control** 2.3% **Leukemia** RR 2.1 (95% CI 0.8–5.6) **Lymphoma** RR 1.0 (95% CI 0.3–3.0) **Cesarean delivery** **Control** 18.4% **Leukemia** RR 1.0 (95% CI 0.6–1.6) **Lymphoma** RR 1.0 (95% CI 0.8–1.4)
Munoz et al, 2015[14]	**Control** 29.5% (95% CI 27.2–28.6) **Leukemia** 54.5% (95% CI 33.7–75.4) **HL** 15.6% (95% CI 5.0–26.2) **NHL** 7.1% (95% CI 0.0–20.6)	--	--
Reulen et al, 2009[11]	**Leukemia (Control)** 16.7% **HL** 14.2%, OR 0.8 (95% CI 0.5–1.3) **NHL** 13.4%, OR 0.7 (95% CI 0.4–1.2)	**Leukemia (Control)** 13.3% **HL** 12.4%, OR 1.1 (95% CI 0.7–1.8) **NHL** 12.0%, OR 1.2 (95% CI 0.7–2.1)	--
Reulen et al, 2017[19]	--	--	**Cesarean delivery (elective)**

Reference	SAB	TAB	Maternal co-morbidity
			Leukemia (Control) 15.2% **HL** 10.3%, RR 0.6 (95% CI 0.3–1.1) **NHL** 18.7%, RR 1.1 (95% CI 0.6–1.8) **Cesarean delivery (emergency)** **Leukemia (Control)** 18.6% **HL** 12.2%, RR 0.6 (95% CI 0.4–1.0) **NHL** 21.3%, RR 1.0 (95% CI 0.7–1.6) **HTN complicating pregnancy** **Leukemia (Control)** 8.9% **HL** 6.5%, RR 0.6 (95% CI 0.3–1.3) **NHL** 11.7%, RR 1.2 (95% CI 0.6–2.3) **HTN complicating pregnancy (excluding preexisting HTN)** **Leukemia (Control)** 5.6% **HL** 3.9%, RR 0.6 (95% CI 0.2–1.6) **NHL** 8.1%, RR 1.3 (95% CI 0.6–3.0) **Gestational diabetes** **Leukemia (Control)** 2.0% **HL** 3.3%, RR 1.3 (95% CI 0.5–3.9) **NHL** 3.6%, RR 1.6 (95% CI 0.5–5.6) **Anemia** **Leukemia (Control)** 5.7% **HL** 6.5%, RR 1.1 (95% CI 0.6–2.1) **NHL** 7.2%, RR 1.2 (95% CI 0.6–2.5) **Malpresentation** **Leukemia (Control)** 5.1% **HL** 5.9%, RR 1.1 (95% CI 0.5–2.5) **NHL** 3.6%, RR 0.7 (95% CI 0.3–1.8) **Postpartum hemorrhage** **Leukemia (Control)** 10.2% **HL** 11.8%, RR 1.0 (95% CI 0.6–1.7) **NHL** 9.0%, RR 0.8 (95% CI 0.4–1.7)
Winther et al, 2008[12]	**Control** 6.0% **Leukemia** 6.3%, PR 1.2 (95% CI 0.7–2.0) **Lymphomas** 7.3%, PR 1.2 (95% CI 0.8–2.0)	--	--
Winther et el, 2009[15]	--	**Control** 18.8% **General Population** 19.7%, PR 1.07 (95% CI 1.01–1.14) **Leukemia** 19.6%, PR 1.0 (95% CI 0.8–1.4) **Lymphoma** 22.0%, PR 1.2 (95% CI 0.9–1.5)	--
Zynda et al, 2012[13]	**Control** 15.0% **Leukemia** 13.2%	**Control** 17.0% **Leukemia** 6.6%	--

APR – Adjusted prevalence ratio (adjusted for year of birth, maternal age, race/ethnicity, mother's education, previous live births, marital status, and maternal smoking during pregnancy), ARR - Adjusted relative risk (adjusted for aboriginal status, previous cesarean delivery, maternal smoking, use of fertility treatment, residential remoteness, and hospital status), CI - Confidence interval, HL - Hodgkin's lymphoma, HTN - Hypertension, NHL - Non-Hodgkin's lymphoma, OR - Odds ratio, PR - Proportion ratio, RR - Relative risk, SAB - Spontaneous abortion, TAB - Therapeutic abortion

-- - Outcome not measured in the study for leukemia/lymphoma survivors

Table III

Summary of Findings for Fetal and Child Health Outcomes

Reference	Live birth	Stillbirth	Preterm birth (<37 weeks)	LBW (<2500 grams) and SGA	Birth defects	Childhood cancer risk
Anderson et al, 2017[17]	**Low Apgar score (<7)** **Control** 2% **HL** 2% APR 0.9 (95% CI 0.3–2.8) **HL chemotherapy (no radiation)** APR 1.9 (95% CI 0.6–5.6) **NHL** 5% APR 2.1 (95% CI 0.9–4.9) **NHL chemotherapy (no radiation)** APR 2.1 (95% CI 0.7–6.4)	--	**<37 weeks** **Control** 9% **HL** 15% APR 1.6 (95% CI 1.1–2.4) **HL radiation (no chemotherapy)** APR 6.0 (95% CI 3.1–11.6) **HL chemotherapy (no radiation)** APR 1.6 (95% CI 0.9–2.9) **HL radiation and chemotherapy** APR 1.0 (95% CI 0.5–2.2) **NHL** 20% APR 2.1 (95% CI 1.4–3.1) **NHL chemotherapy (no radiation)** APR 2.7 (95% CI 1.7–4.3) **NHL radiation and chemotherapy** APR 2.6 (95% CI 1.2–5.9) **<34 weeks** **Control** 2% **HL** 2% APR 1.3 (95% CI 0.5–3.4) **HL chemotherapy (no radiation)** APR 2.1 (95% CI 0.7–6.1) **NHL** 10% APR 3.4 (95% CI 1.9–6.2) **NHL chemotherapy (no radiation)** APR 4.2 (95% CI 2.2–8.3)	**LBW** **Control** 7% **HL** 10% APR 1.4 (95% CI 0.9–2.3) **HL radiation (no chemotherapy)** APR 4.6 (95% CI 1.9–11.1) **HL chemotherapy (no radiation)** APR 1.4 (95% CI 0.7–2.9) **HL radiation and chemotherapy** APR 0.9 (95% CI 0.4–2.3) **NHL** 19% APR 2.4 (95% CI 1.6–3.7) **NHL chemotherapy (no radiation)** APR 3.3 (95% CI 2.1–5.3) **NHL radiation and chemotherapy** APR 1.8 (95% CI 0.5–7.1) **SGA** **Control** 10% **HL** 12% APR 1.1 (95% CI 0.7–1.6) **HL chemotherapy (no radiation)** APR 1.0 (95% CI 0.5–1.9) **HL radiation and chemotherapy** APR 1.3 (95% CI 0.7–2.2) **NHL** 12% APR 1.1 (95% CI 0.7–1.8) **NHL chemotherapy (no radiation)** APR 1.3 (95% CI 0.7–2.4)	--	--
Green et al, 2002[10]	**Control** 70.9 % **Leukemia** 62.4%, RR 0.6 (95% CI 0.5–0.8) **HL** 66.4%, RR 0.8 (95% CI 0.7–0.9) **NHL** 66.7%, RR 0.8 (95% CI 0.6–1.1)	**Control** 0.7% **Leukemia** 1.2%, RR 1.7 (95% CI 0.6–4.5) **HL** 1.0%, RR 1.6 (95% CI 0.6–4.0) **NHL** 1.3%, RR 2.0 (95% CI 0.6–6.1)	--	--	--	--

Leuk Lymphoma. Author manuscript; available in PMC 2019 February 01.

Reference	Live birth	Stillbirth	Preterm birth (<37 weeks)	LBW (<2500 grams) and SGA	Birth defects	Childhood cancer risk
Haggar et al, 2014[18]	**Low Apgar score (<7)** **Leukemia** ARR 1.5 (95% CI 0.8–3.2) **Lymphoma** ARR 1.0 (95% CI 0.5–1.9) **Neonatal resuscitation** **Leukemia** ARR 0.3 (95% CI 0.4–2.5) **Lymphoma** ARR 1.5 (95% CI 0.4–5.8)	--	**Leukemia** ARR 1.7 (95% CI 1.2–2.4) **Lymphoma** ARR 0.9 (95% CI 0.4–2.3)	**LBW** **Leukemia** ARR 1.8 (95% CI 1.4–2.6) **Lymphoma** ARR 0.87 (95% CI 0.3–2.4)	--	--
Hawkins et al, 1995[22]	--	--	--	--	**Death from birth defect** Observed: 1 case Expected: 0.7 cases RR 0/E 1.4 (95% CI 0.03–7.5) **Sex ratio (M:F)** **Survivor** 1.4, p=0.06 compared to controls	Observed: 0 cases Expected: 0.4 cases RR O/E 0.0 (95% CI 0.0–8.4)
Kenney et al, 1996[23]	--	--	--	--	**Sex ratio (M:F)** **Control** 0.8 **Leukemia** 1.2, RR 1.2 (95% CI 0.9–1.6) **Birth defects** **Control** 3.5% **Leukemia** 3.6%, RR 1.0 (95% CI 0.3–3.1) **Cyclophosphamide exposure (>1g/m^2)** OR 4.6 (95% CI 0.5–57.0) **Anthracycline exposure** OR 2.1 (95% CI 0.2–19.6) **Radiation** OR 0.3 (95% CI 0.03–17.3)	--
Madanat-Harjuoja et al, 2010[26]	--	--	--	--	--	**Leukemia** SIR (all cases) 1.7 (95% CI 0.8–3.0); SIR (sporadic cases) 1.7 (95% CI 0.8–3.0) **NHL** SIR (all cases) 0.80 (95% CI 0.1–2.9); SIR (sporadic cases) 0.8 (95% CI 0.1–2.9) **HL** SIR (all cases) 0.9 (95% CI 0.1–3.1); SIR (sporadic cases) 0.4 (0.01–2.4)
Mueller et al, 2009[16]	--	--	**Control** 10.3% **Leukemia** RR 2.6 (95% CI 1.8–3.6) **Lymphoma** RR 1.8 (95% CI 1.3–2.5)	**LBW** **Control** 7.6% **Leukemia** RR 1.5 (95% CI 1.0–2.1)	--	--

Reference	Live birth	Stillbirth	Preterm birth (<37 weeks)	LBW (<2500 grams) and SGA	Birth defects	Childhood cancer risk
				Lymphoma RR 1.0 (95% CI 0.7–1.5)		
Munoz et al, 2015[14]	**Control** 39.3% (95% CI 38.7–39.8) **Leukemia** 20.4% (95% CI 9.1–31.7) **HL** 50.0% (95% CI 38.8–61.2) **NHL** 54.2% (95% CI 34.2–74.1)	--	--	--	--	--
Reulen et al, 2009[11]	**Leukemia (Control)** 69.4% **HL** 72.5%, OR 1.2 (95% CI 0.8–1.8) **NHL** 74.6%, OR 1.4 (95% CI 0.9–2.4) **Observed/Expected in general population (O/E)** **Leukemia** O/E 0.6 (95% CI 0.6–0.7) **HL** 0/E 0.9 (95% CI 0.8–0.9) **NHL** O/E 0.8 (95% CI 0.7–0.9)	**Leukemia (Control)** 0.6% **HL** 0.9%, OR 1.4 (95% CI 0.3–5.7) **NHL** 0%	**Leukemia (Control)** 12.9% **HL** 11.6%, OR 0.9 (95% CI 0.5–1.6) **NHL** 13.4%, OR 1.1 (95% CI 0.6–2.0)	**LBW** **Leukemia (Control)** 6.2% **HL** 5.5%, OR 1.0 (95% CI, 04–2.3) **NHL** 11.1%, OR 2.1 (95% CI 1.0–4.8)	--	--
Reulen et al, 2017[19]	--	**Leukemia (Control)** 0.7% **HL** 0% **NHL** 0.9%	**Leukemia (Control)** 11.6% **HL** 5.3%, RR 0.4 (95% CI 0.2–1.0) **NHL** 15.6%, RR 1.3 (95% CI 0.7–2.4)	**LBW** **Leukemia (Control)** 9.1% **HL** 3.6%, RR 0.4 (95% CI 0.2–1.2) **NHL** 7.8%, RR 0.9 (95% CI 0.4–2.0)	--	--
Sankila et al, 1998[25]	--	--	--	--	--	**Leukemia** 1.7%, SIR 0.9 (95% CI 0.2–2.5) **NHL** 0.3%, SIR 3.1 (95% CI 0.6–9.2)
Signorello et al, 2006[20]	--	--	**Control** 12.6% **Leukemia** 18.8% **HL** 19.2% **NHL** 20.9%	**LBW** **Control** 4.2% **Leukemia** 9.4% **HL** 5.9% **NHL** 10.1% **SGA** **Control** 9.2% **Leukemia** 9.8% **HL** 9.0% **NHL** 9.7%	--	--
Swerdlow et al, 1996[21]	--	--	**Control** 7.1% **HL** 8.3%, RR 0.9 (95% CI 0.3–2.5)	**LBW** **Control** 6.7% **HL** 10.6%, RR 1.6 (95% CI 0.5–4.3)	**Sex ratio (M:F)** **Control** 1.0 **HL** 0.96, RR 0.9 (95% CI 0.5–1.6)	--
Vernaeve et al, 2007[27]	**Control** 69% **Leukemia** 80%	--	--	--	--	--

Reference	Live birth	Stillbirth	Preterm birth (<37 weeks)	LBW (<2500 grams) and SGA	Birth defects	Childhood cancer risk
	HL 71.4% **NHL** 100%					
Winther et al, 2003[24]	--	--	--	--	**Sex ratio (M:F)** **Control** 1.1 **Leukemia** Non-irradiated parent 0.9 Irradiated parent 1.4 RR irradiated to non-irradiated 1.5 (95% CI 0.6–3.8) **Lymphoma** Non-irradiated 1.2 Irradiated 1.1 RR irradiated to non-irradiated 0.9 (0.4–1.8)	--

APR – Adjusted prevalence ratio (adjusted for year of birth, maternal age, race/ethnicity, mother's education, previous live births, marital status, and maternal smoking during pregnancy), ARR - adjusted relative risk (adjusted for aboriginal status, previous cesarean delivery, maternal smoking, use of fertility treatment, residential remoteness, and hospital status), CI - Confidence interval, HL - Hodgkin's lymphoma, LBW - Low birth weight, NHL - non-Hodgkin's lymphoma, OR - Odds ratio, PR - proportion ratio, RR - Relative risk, SGA - small for gestational age, SIR - Standardized incidence ratio

-- - Outcome not measured in the study for leukemia/lymphoma survivors

Table IV

Summary of Maternal Pregnancy and Fetal/Child Health Outcomes for Leukemia and Lymphoma Survivors Compared to Healthy Controls

Outcomes		Healthy controls (%)	Leukemia			Lymphoma		
			Absolute risk (%)	Relative change in risk	Direction of risk	Absolute risk (%)	Relative change in risk	Direction of risk
Maternal	Spontaneous Abortion	6.0–15.0	6.0–14.0[^]	1.2[^]	↔[^]	7.0–16.0	1.1–1.2	↔
	Pregnancy Termination	12.0–20.0	7.0–20.0	1.0–1.7	?	15.0–22.0	1.3	?
	Anemia in Pregnancy	2.0	--	2.1	↔	--	1.0	↔
	Diabetes in Pregnancy	1.4	--	1.2–1.5	↔	--	0.4–1.5	↔
	Cesarean Deliveries	18.0–33.0	--	1.0–2.0	?	33.0–42.0	1.0–1.5	↔
Fetal and Child Health	Live Birth	71.0	62.0	0.6	↓	66.0–67.0	0.8–0.9	↓
	Stillbirth	0.7	1.2	1.7	↔	1.0–1.3	1.6–2.0	↔
	Preterm Birth (<37 weeks; <34 weeks)	7.0–13.0; 2.0[v]	19.0; --	1.7–2.6; --	↑	8.0–21.0; 2.0–10.0[v]	0.9–2.1; 1.3–3.4[v]	↑
	LBW(<2500 grams)	4.0–8.0	9.0	1.5–1.8	↑	6.0–19.0	0.9–2.4	↑
	SGA	9.0–10.0	10.0	--	↔	9.0–12.0	1.1	↔
	Birth Defects	3.5	3.6	1.0–1.4	↔	--	1.4	↔
	Offspring Sex Ratio (M:F)	0.8–1.1	0.9–1.4	0.8–0.9	↔	1.1–1.2	0.9–1.4	↔
	Childhood Cancer Risk	--	1.7	0.9–1.7[*]	↔	0.3	0.8–3.1[*]	↔

Note: pregnancies achieved by donor oocytes were excluded

↑ - Increased, ↓ - Decreased, ↔ - No difference, ? - Inconsistent data, -- Data not available

[^] Acute lymphoblastic leukemia patients exposed to cranial and spinal radiation (absolute risk - 28% absolute risk; relative risk - 3.6)

[v] Preterm birth (<34 weeks)

[*] Standard incidence ratio