Retrospective Cohort Study of Phototherapy and Childhood Cancer in Northern California

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abstract

OBJECTIVE: To investigate the association between neonatal phototherapy use and childhood cancer.

METHODS: This retrospective cohort study included 499 621 children born at ≥35 weeks' gestation from 1995 to 2011 in Kaiser Permanente Northern California hospitals, who survived to hospital discharge and were followed ≥60 days. We obtained data on home and inpatient phototherapy, covariates, and cancer incidence from electronic records. We used propensity-adjusted Cox and Poisson models to control for confounding and unequal follow-up times.

RESULTS: There were 60 children with a diagnosis of cancer among 39 403 exposed to phototherapy (25 per 100 000 person-years), compared with 651 of 460 218 unexposed children (18 per 100 000 person-years; incidence rate ratio [IRR] 1.4; P = .01). Phototherapy was associated with increased rates of any leukemia (IRR 2.1; P = .0007), nonlymphocytic leukemia (IRR 4.0; P = .0004), and liver cancer (IRR 5.2; P = .04). With adjustment for a propensity score that incorporated bilirubin levels, chromosomal disorders, congenital anomalies, and other covariates, associations were no longer statistically significant: Adjusted hazard ratios (95% confidence intervals) were 1.0 (0.7–1.6) for any cancer, 1.6 (0.8–3.5) for any leukemia, 1.9 (0.6–6.9) for nonlymphocytic leukemia, and 1.4 (0.2–12) for liver cancer. Upper limits of 95% confidence intervals for adjusted 10-year excess risk were generally <0.1% but reached 4.4% for children with Down syndrome.

CONCLUSIONS: Although phototherapy use was associated with increased cancer rates (particularly nonlymphocytic leukemia), control for confounding variables eliminated or attenuated the associations. Nonetheless, the possibility of even partial causality suggests that avoiding unnecessary phototherapy may be prudent.

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WHAT'S KNOWN ON THIS SUBJECT: Phototherapy can cause DNA damage in vivo and in vitro. However, epidemiologic studies relating neonatal phototherapy to cancer risk in infancy and childhood have had mixed results.

WHAT THIS STUDY ADDS: Although we confirmed that phototherapy use is associated with increased risk of childhood cancer, particularly nonlymphocytic leukemia, our results suggest that this association results at least partly from confounding by variables associated with both phototherapy use and cancer risk.

ARTICLE

Phototherapy is widely used to treat hyperbilirubinemia in newborns. Although it is generally regarded as safe,[1,2] the number needed to treat to prevent 1 infant from reaching exchange transfusion levels may be >1000,[3] and very few of those reaching exchange levels have adverse effects.[4–8] Thus, even rare adverse effects of phototherapy could warrant changes in treatment thresholds.[9]

Concerns about a possible carcinogenic effect of neonatal phototherapy date back to the 1970s, when Speck and Rosenkranz[10] reported positive results on the Ames test for mutagenicity of blue light in salmonellae. More recent studies have confirmed DNA damage in vivo from phototherapy.[11-14] Epidemiologic studies have focused on leukemia. Three studies from northern Europe found no association.[15-17] In contrast, a Washington State study[18] reported an adjusted odds ratio (OR) of 2.5 (95% confidence interval [CI], 1.0–6.2) for all childhood leukemias (excluding infants with Down syndrome), and a Swedish matched case–control study[19] reported an OR of 7.5 (95% CI, 1.8–31.9) for myelogenous leukemia. After infants with Down syndrome were excluded from the Swedish study, the association was no longer statistically significant (OR 4.3; 95% CI, 0.9–21.9).

In the California Late Impact of Phototherapy Study, which used linked birth certificates and discharge abstracts, Wickremasinghe et al[20] reported statistically significant propensity-adjusted ORs for any cancer, myeloid leukemia, kidney, and other cancer diagnoses before age 1 year. A limitation of that study is that follow-up was only 1 year, raising the question of whether the increased risk persists. A limitation shared with previous studies is lack of data on bilirubin levels, limiting ability to control for confounding by indication. This report from the Late

Impact of Getting Hyperbilirubinemia or Phototherapy study investigates the associations between neonatal phototherapy use and cancer in a large Kaiser Permanente Northern California (KPNC) cohort, with up to 19 years of follow-up and measurements of bilirubin levels and other potential confounding variables from the electronic medical record.

METHODS

Study Design, Subjects, and Approvals

The Late Impact of Getting Hyperbilirubinemia or Phototherapy study is a retrospective cohort study of 525 409 children born at ≥35 weeks' gestation from January 1, 1995 through December 31, 2011 at 15 KPNC hospitals. We excluded 344 infants (0.07%) who died during their birth hospitalization, 891 (0.17%) whose birth hospitalization ended with a transfer out of the KPNC system, 24 532 (4.7%) who were followed <60 days, and 21 (<0.01%) with a first cancer diagnosis before 60 days, leaving a cohort of 499 621 infants.

The institutional review boards for the protection of human subjects at the University of California, San Francisco and KPNC approved the study.

Phototherapy

For children born before implementation of the Epic (Verona, WI) electronic medical record (80% of subjects), we identified those who received inpatient phototherapy from procedure codes (99.82 and 99.83) for admissions before age 30 days. For children born after implementation of Epic, we classified infants as having received inpatient phototherapy if they had either a phototherapy nursing flow sheet or both a procedure code and an order for phototherapy. We ascertained home phototherapy from the KPNC durable medical equipment database.

Because we did not have reliable data on the duration or intensity of phototherapy, the primary prespecified predictor variable for all analyses was a dichotomous variable for any phototherapy, whether provided in the hospital, at home, or both. To investigate a dose-–response relation we created a phototherapy dosage variable with values of 0 for no phototherapy, 1 for home phototherapy only, 2 for phototherapy during 1 admission, and 3 for phototherapy during 2 or more admissions.

Covariates

We obtained covariates from electronic records, including gender, race and ethnicity, maternal age, delivery mode, multiple birth, birth weight, gestational age, Apgar scores, and total serum bilirubin (TSB) levels. To optimize control for confounding, we assessed each TSB level in relation to the 2004 American Academy of Pediatrics (AAP) phototherapy guidelines[21] by using direct antiglobulin test and gestational age to determine the neurotoxicity risk group, as previously described.[3] We determined whether each subject had ≥1 TSB level between −3 and +4.9 mg/dL from the appropriate AAP phototherapy threshold and, if so, created a variable equal to the difference (in 1-mg/dL categories) between the first such TSB level and the phototherapy threshold.

We identified subjects with genetic disorders and congenital anomalies based on International Classification of Diseases, Ninth Revision (ICD-9) codes from inpatient and outpatient encounters; we required ≥2 encounters with the same ICD-9 code to reduce false-positive diagnoses due to coding errors. We created dichotomous variables for Down syndrome (758.0), other chromosomal abnormalities (758.1–758.9), and congenital anomalies diagnosed at <15 days (740–759.9

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except 743.65 [nasolacrimal passage anomaly]).

Follow-up Time

For purposes of quantifying incidence rates and use of proportional hazards models, follow-up began at age 60 days and ended at death, the date of the first diagnosis of cancer, or the last follow-up date, defined as the last day of the last calendar month of coverage by the KPNC health plan or the last encounter date through March 11, 2014, whichever came later.

Outcome Variables

We identified cancer cases from the KPNC tumor registry and the KPNC Virtual Data Warehouse, which captures diagnoses from all inpatient and outpatient encounters. For children not in the tumor registry, we required ≥2 encounters with diagnoses of cancer (ICD-9 codes 140–209.36) or carcinoma in situ (230–234.9). We confirmed diagnoses of leukemia, kidney, bone, and liver cancer by medical record review.

We included only the first diagnosis of cancer in each child. We grouped cancers into the following categories: lymphocytic leukemia, myelocytic leukemia, nonlymphocytic leukemia, other leukemia, brain and nervous system, liver, kidney, bone, skin, and other cancers. We excluded subjects whose first diagnosis of cancer was made before 60 days, to reduce the possibility of finding associations due to preexisting cancer.

Statistical Analysis

We created datasets by using SAS 9.4 (SAS Institute, Inc, Cary, NC), and performed statistical analyses by using Stata 13 (Stata Corp, College Station, TX) and SAS 9.4.

We compared children who did and did not receive any phototherapy by using descriptive statistics with χ^2 and analysis of variance tests, as appropriate. We calculated incidence

rates by dividing the number of cancer cases by person-years of follow-up. To compare KPNC cancer incidence rates with California statewide data (obtained from CDC Wonder[22]), we standardized California rates to the age distribution of follow-up in the KPNC cohort used for this study.

We investigated which variables were independently associated with each cancer type by using backward stepwise Cox models, keeping terms with $P < .1$, and forcing phototherapy into all models. Candidate covariates, selected based on associations with childhood cancer in previous studies, were gender, race or ethnicity (in 5 categories), birth weight (in 6 categories), maternal age ≥35 years, multiple birth, Down syndrome, other chromosomal abnormalities, congenital anomalies, and 5-minute Apgar score <7. In addition, to investigate confounding by indication we included candidate predictors for the AAP risk group (low, medium, and high),[21] early jaundice (defined as a TSB within 3 mg/dL of the AAP phototherapy threshold at <24 hours), and a dichotomous

variable for ever exceeding the AAP phototherapy threshold. We did not include the maximum TSB level as a candidate predictor because it could be affected by phototherapy and thus act as a possible mediator or collider (see directed acyclic graph in the Supplemental Fig 4).

Propensity-adjusted analyses control for measured confounding variables by creating a model for the probability of exposure (in this case, phototherapy) and then controlling for that probability. When the exposure is more common than the outcome, this allows control for more possible confounding variables.

We created 2 propensity models for our primary predictor (any phototherapy). Our restricted model (the prespecified primary analysis) included only subjects with ≥1 TSB level between −3 and +4.9 mg/dL from the AAP phototherapy threshold. We included indicator variables for the difference between the first such TSB level and the AAP threshold in 1-mg/dL intervals (eg, −3 to −2.1 mg/dL) and the age (in days) at which it occurred, as
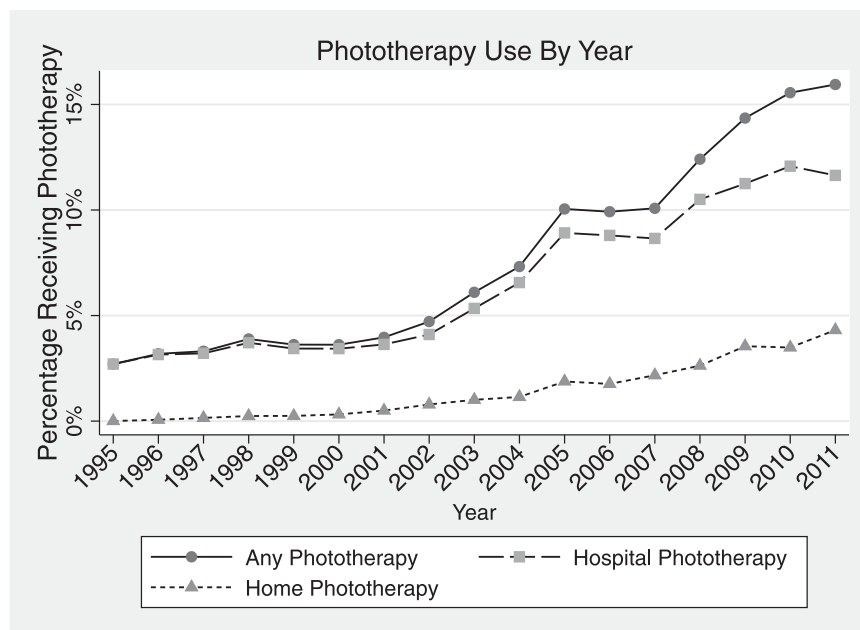

FIGURE 1
Phototherapy use among study subjects by year of birth.

explained in our previous studies.[3,23] This restricted model has the advantage that it includes only infants in whom the probability of receiving phototherapy is not close to 0 or 1, a requirement for validity of propensity-adjusted analyses.[24] Our inclusive model had the advantage that it included all subjects. It used the same bilirubin variables as the stepwise Cox models described earlier.

To create these propensity scores, we used forward stepwise logistic regression models with P to enter <0.05 and P to remove >0.05. Based on previous research, we forced the following variables into propensity models: gender, gestational age, birth weight, Down syndrome, other chromosomal abnormalities, congenital anomalies, and 5-minute Apgar score <7. Additional candidate predictors included those previously listed for backward stepwise models for cancer as well as hospital and year of birth and all 2-way interactions. (The computational intensity of including all possible 2-way interactions necessitated forward stepwise models.) Our final propensity models were selected based on negligible improvement (<0.001) in a cross-validated area under the receiver operating characteristic curve. Propensity scores were entered in multivariate Cox models as either quintile indicators or restricted cubic splines. We created the propensity score for ≥2 phototherapy admissions by using the bilirubin variables from the restricted model, gestational age, delivery mode, and variables significant in any of the stepwise Cox models described earlier.

The Cox model provides hazard ratios (HRs) but not estimates of absolute risk. To estimate phototherapy-associated absolute risk increases and their 95% CIs, we used Poisson models adjusting for the restricted model propensity score. Because the baseline risk in children with Down syndrome is so much higher than in the general population, we created these models and estimated marginal 10-year risk differences and 95% CIs separately in children with and without Down syndrome. We accounted for clustering by hospital by using robust standard errors in all analyses.

RESULTS

Phototherapy Exposure and Description of Study Subjects

Use of phototherapy increased during the course of this study, from 2.7% in 1995 to 15.9% in 2011 (Fig 1). Most infants received phototherapy in the hospital, during the birth admission only (N = 23 284), a readmission only (N = 10 498), or both (N = 854); only 5003 received phototherapy at home only. As expected, infants exposed to phototherapy had more risk factors for hyperbilirubinemia (Table 1). Exposed infants were also much more likely to have Down syndrome, another chromosomal disorder, or a congenital anomaly.

Crude Cancer Incidence Rates

Because phototherapy use increased during the study period, mean (±SD) follow-up time was shorter in infants who had received phototherapy (6.2 ± 4.3 years) than in those who had not (8.3 ± 5.2 years). A total of 711 children were diagnosed with cancer

TABLE 1 Demographic and Clinical Characteristics of Infants Exposed to Phototherapy and 2 Groups of Unexposed Infants

	Phototherapy	No Phototherapy	
		≥1 TSB −3 to 4.9 mg/dL From Phototherapy Threshold	No TSB −3 to 4.9 mg/dL From Phototherapy Threshold
Number of infants	39 403	62 592	397 626
Year of birth ≥2003, %	79.2	66.1	50.8
Male, %	56.0	53.8	50.2
Race, %			
White	34.0	38.7	43.7
Black	4.9	5.1	8.5
Asian	30.4	24.8	16.6
Hispanic	23.6	24.2	24.2
Other or unknown	7.2	7.1	7.0
Down syndrome, %	0.53	0.21	0.05
Other chromosomal anomaly, %	0.3	0.2	0.1
Congenital anomaly, %	3.8	2.4	1.8
Birth wt, mean ± SD, g	3260 ± 589	3354 ± 526	3467 ± 493
Birth wt ≥4500 g, %	1.9	1.9	2.2
Gestational age, mean ± SD, wk	38.2 ± 1.7	38.6 ± 1.6	39.3 ± 1.3
5-minute Apgar <7, %	1.6	0.8	0.8
Maximum TSB, mean ± SD, mg/dL	16.5 ± 3.8	15.2 ± 3.3	N/A
Maximum TSB, mg/dL, %			
Not done or not found	0.4	0.0	61.7
<10	3.2	8.3	24.3
10–14.9	29.5	33.5	11.9
15–19.9	50.1	53.4	2.2
20–24.9	15.7	4.7	0.0
≥25	1.2	0.1	0.0
Direct antiglobulin test result, %			
Positive	11	6	1
Negative	58	50	31
Not done	31	43	68
Follow-up, y	6.2 ± 4.3	7.3 ± 4.9	8.4 ± 5.3

P values comparing the 3 phototherapy exposure groups with χ^2 or ANOVA tests were <.001 for all variables in the table. N/A, not applicable.

TABLE 2 Incidence of Cancer Diagnosed at ≥ 60 d per 100 000 Person-Years by Use of Phototherapy in KPNC, Compared With California Statewide Rates

	Total Cases	Total KPNC IR	CA IR	Phototherapy		No Phototherapy		Crude IRR (95% CI)	P[a]
				Cases	IR	Cases	IR		
Any cancer	711	17.6	17.7	60	25.2	651	17.5	1.4 (1.1–1.9)	.010
Any leukemia	223	5.5	6.5	27	11.4	196	5.3	2.1 (1.4–3.2)	.0007
Lymphocytic	169	4.2	5.1	16	6.7	153	4.1	1.6 (0.9–2.7)	.08
Nonlymphocytic leukemia	54	1.3	1.4	11	4.6	43	1.2	4.0 (1.8–7.8)	.0004
Myelocytic	36	0.9	1.0	7	2.9	29	0.8	3.7 (1.4–8.7)	.006
Other nonlymphocytic leukemia	18	0.4	0.4	4	1.7	14	0.4	4.4 (1.1–14)	.02
Brain and nervous tissue	152	3.8	4.6	6	2.5	146	3.9	0.6 (0.2–1.4)	.28
Skin	29	0.7	N/A	2	0.8	27	0.7	1.2 (0.1–4.6)	.79
Kidney	26	0.6	1.0	4	1.7	22	0.6	2.8 (0.7–8.3)	.09
Bone	13	0.3	0.5	2	0.8	11	0.3	2.8 (0.3–13)	.22
Liver	12	0.3	0.4	3	1.3	9	0.2	5.2 (0.9–21)	.04
All others	256	6.3	N/A	16	6.6	240	6.6	1.0 (0.6, 1.7)	.86

CA, California; IR, incidence rate per 100 000 person-years; N/A, not applicable, because CDC Wonder does not include skin cancers.

[a] By exact, 2-tailed test.

after 60 days of age, a rate of 17.6 per 100 000 person-years. Total and site-specific cancer incidence rates were similar to California rates (Table 2).[22]

There were 60 cancer cases (24.6 per 100 000 person-years) among children exposed to phototherapy, compared with 651 cases (17.2 per 100 000 person-years) among unexposed children. Crude incidence rate ratios (IRRs) were elevated, with $P < .05$ for any cancer, any leukemia, myelocytic leukemia, other leukemia, and liver cancer, with slightly higher P values (.05 < $P < .10$) for lymphocytic leukemia and kidney cancer (Table 2). There was no evidence that any of these IRRs varied by year of birth (in three 5- to 6-year groups). Although total cancer and total leukemia showed approximately constant hazards in both exposed and unexposed infants, the excess of nonlymphocytic leukemia occurred early (<3 years), whereas the excess lymphocytic leukemia cases began later (Fig 2).

Multivariate Models

Backward stepwise Cox regression models yielded lower HRs and higher P values than unadjusted analyses (Table 3). Variables related to hyperbilirubinemia were associated with nonlymphocytic leukemia, any leukemia, and kidney cancer, indicating the potential for confounding by indication. Down syndrome was a powerful risk factor for any cancer (HR 14.4) and for leukemia (HR 45.9) but not for kidney, bone, or liver cancer. Other risk factors for cancer included high birth weight, 5-minute Apgar <7, other chromosomal disorders, and congenital anomalies. The full adjusted Cox models for all cancer types are provided in Supplemental Table 5.

Crude IRRs and adjusted HRs with 95% CIs are shown in Fig 3 for cancers at sites associated with phototherapy in this or other
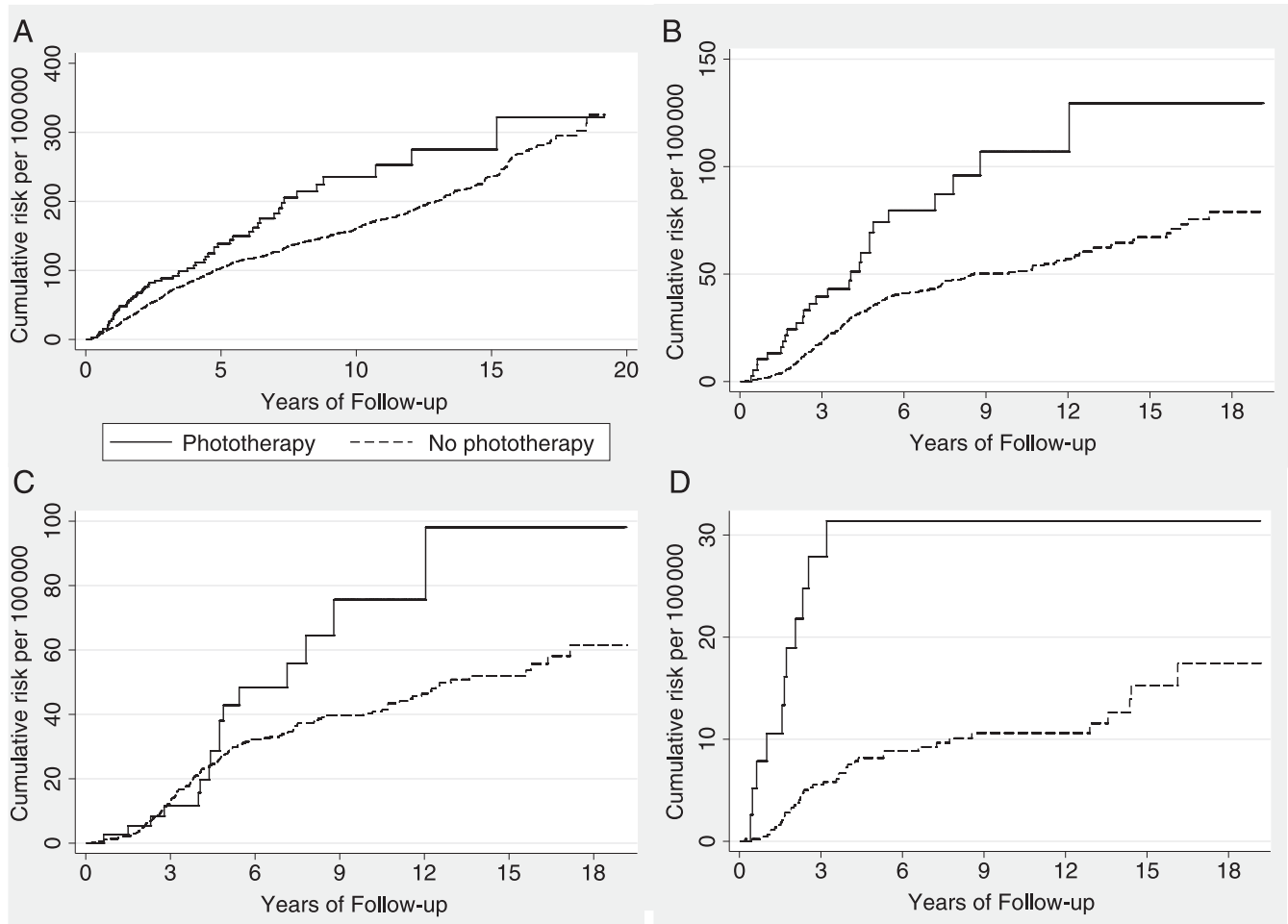
FIGURE 2
Crude cumulative incidence of cancer by phototherapy use in children at KPNC born 1995–2011. A, Any cancer; B, Any leukemia; C, Lymphocytic leukemia; D, Nonlymphocytic leukemia. Note that the scale for cumulative risk per 100 000 ranges from a maximum of 30 in Fig 2D to a maximum of 400 in Fig 2A. Differences were not statistically significant in multivariable models.

studies. With propensity adjustment based on either the restricted or inclusive model (not shown) and coding propensity based on either quintiles or splines (not shown), all associations were attenuated and lost statistical significance. Most HRs were slightly more attenuated when subjects with propensity scores <0.05 or >0.95 were excluded. Data for Fig 3, including some models not shown there, are provided in Supplemental Table 6. The highest HRs after propensity adjustment in the prespecified restricted model were for nonlymphocytic leukemia (HR 1.94; 95% CI, 0.55–6.92; *P* = .31) and kidney cancer (HR 3.57; 95% CI, 0.22–58.3; *P* = .37). Hazard ratios were similar whether phototherapy

was administered during the birth hospitalization or a readmission. Hazard ratios tended to be lower for home phototherapy only, but CIs were wide. For example, the adjusted HR for home (only) phototherapy for all cancer was 0.47 (95% CI, 0.14–1.54).

The phototherapy dose variable was not statistically significantly associated with total cancer or any type of cancer when entered as a single variable. The receipt of phototherapy during ≥2 admissions was associated with nonlymphocytic leukemia in the model adjusted for propensity to have ≥2 phototherapy admissions (HR 8.5; 95% CI, 1.9–38; *P* = .006) and a backward

stepwise Cox model (HR 5.1; 95% CI, 1.06–24.7; *P* = .04) even though the number of exposed cases was only 2 (both with acute myelogenous leukemia).

For children without Down syndrome, upper limits of 95% CIs suggested that the 10-year adjusted absolute risk increase for any leukemia or any cancer among children receiving phototherapy is likely to be <100/100 000 (0.1%), corresponding to a number needed to harm of >1000 (Table 4). In children with Down syndrome, because of their higher baseline risk of cancer, the same upper limit of the IRR translates into a 10-year excess risk of up to 4.4% for leukemia,

TABLE 3 Hazard Ratios (95% CIs) for Cancer for Phototherapy and Other Perinatal Risk Factors Identified Using Backward Stepwise Cox Models With $P < .1$[a]

Risk Factor	Any Cancer (N = 711)	Any Leukemia (N = 223)	Lymphocytic Leukemia (N = 169)	Nonlymphocytic Leukemia (N = 54)	Kidney Cancer (N = 26)	Bone Cancer (N = 13)	Liver Cancer (n = 12)
Any phototherapy	1.28 (0.92–1.77)	1.33 (0.94–1.89)	1.15 (0.80–1.67)	1.09 (0.64–1.84)	1.34 (0.70–2.56)	3.30 (0.60–18.3)	3.44[b] (1.13–10.5)
Down syndrome	14.4[c] (9.41–22.2)	45.9[c] (30.0–70.2)	31.1[c] (14.0–69.5)	139[c] (66.0–293)	NI	NI	NI
Other chromosomal disorders	4.71[c] (2.71–8.20)	2.70[b] (1.14–6.36)	NI	NI	NI	30.0[c] (9.19–97.9)	34.8[c] 8.29–146)
Congenital anomalies	1.52[b] (1.11–2.08)	NI	NI	NI	8.79[c] (3.23–23.9)	3.27[d] (0.95–11.3)	NI
Apgar <7 at 5 min	1.91[b] (1.06–3.43)	2.69[b] (1.18–6.13)	2.54[d] (0.86–7.54)	NI	NI	NI	7.08[b] (1.73–29.0)
Male gender	NI	1.29[e] (1.10–1.51)	1.46[e] (1.17–1.82)	NI	NI	NI	0.44[d] (0.18–1.07)
Maternal age ≥35 y	NI	NI	NI	0.49[b] (0.25–0.95)	NI	NI	NI
Early jaundice	NI	1.75[b] (1.19–2.59)	NI	3.28[e] (1.61–6.66)	NI	NI	NI
Any TSB > AAP phototherapy threshold	NI	NI	NI	2.13[d] (0.95–4.75)	2.09[d] (0.97–4.49)	NI	NI

NI, not included in model; $P \geq .1$

[a] Hazard ratios are included for all risk factors with $P < .1$ except for the 6 birth wt and 5 race categories. Not shown: High birth wt was significantly associated with any cancer, any leukemia, lymphocytic leukemia, and kidney cancer (all $P < .0005$), and black race was associated with decreased risk of any cancer relative to white race (HR = 0.73; $P = .05$). Complete models are provided in the Supplemental Information.

[b] $.005 < P < .05$. The P value for any phototherapy and liver cancer was .03.

[c] $P < .0005$.

[d] $.05 < P < .1$.

[e] $.0005 < P < .005$.

corresponding to a number needed to harm that could be as low as 23. For kidney, bone, and liver cancers (which were not associated with Down syndrome), upper limits of 10-year absolute risk increases were ≤31/100 000 (0.03%), indicating numbers needed to harm of >3200.

TABLE 4 Propensity-Adjusted 10-y Excess Risk of Cancer (95% CI) per 100 000 Newborns Exposed to Phototherapy

	No Down Syndrome		Down Syndrome	
All cancer	1.2	(−89, +91)	26	(−1959, +2011)
All leukemia	27	(−22, +76)	1547	(−1269, +4364)
Lymphocytic	15	(−21, +51)	503	(−820, +1826)
Nonlymphocytic	13	(−16, +42)	1654	(−1102, +4410)
Whole Population				
Kidney	10	(−11, +31)		
Bone	−2	(−12, +7)		
Liver	0	(−18, +18)		

To obtain the number needed to harm (NNH), divide positive numbers shown into 100 000. For example, for all leukemia among infants without Down syndrome, the point estimate for the number of children who would need to be exposed to phototherapy to cause 1 case of leukemia over 10 y (if the association is causal) would be 100 000/27 = 3704, whereas for children with Down syndrome it would be 100 000/1547 = 65.

DISCUSSION

In this retrospective cohort study, we found that increases in incidence of total cancer, leukemia (especially nonlymphocytic leukemia), and liver cancer among children exposed to phototherapy as newborns were no longer statistically significant after adjustment for confounding using either traditional methods or phototherapy propensity scores. Although attenuation of the associations with multivariable analysis suggests confounding is at least a partial explanation for these findings, we must also consider 3 alternative bases for the associations: chance, bias, and effect-cause.[25]

The low P values and consistency with previous studies, particularly the striking early increase in nonlymphocytic leukemia, make chance an unlikely explanation for the crude association between phototherapy and cancer. On the other hand, the wider CIs of the adjusted estimates are consistent with either no or a moderate elevation of the adjusted HR. Bias is unlikely to explain the observed association: Any misclassification of exposure or outcomes in this study is likely to be nondifferential, which would bias rate ratios and HRs toward 1.

Some children are born with cancer, and preexisting cancer could cause illness or higher TSB levels, leading to increased phototherapy rates. For this reason, we excluded 21 subjects with cancers diagnosed before 60 days. It seems unlikely that enough cancers diagnosed at >60 days were already causing hyperbilirubinemia in the newborn period to explain the association.
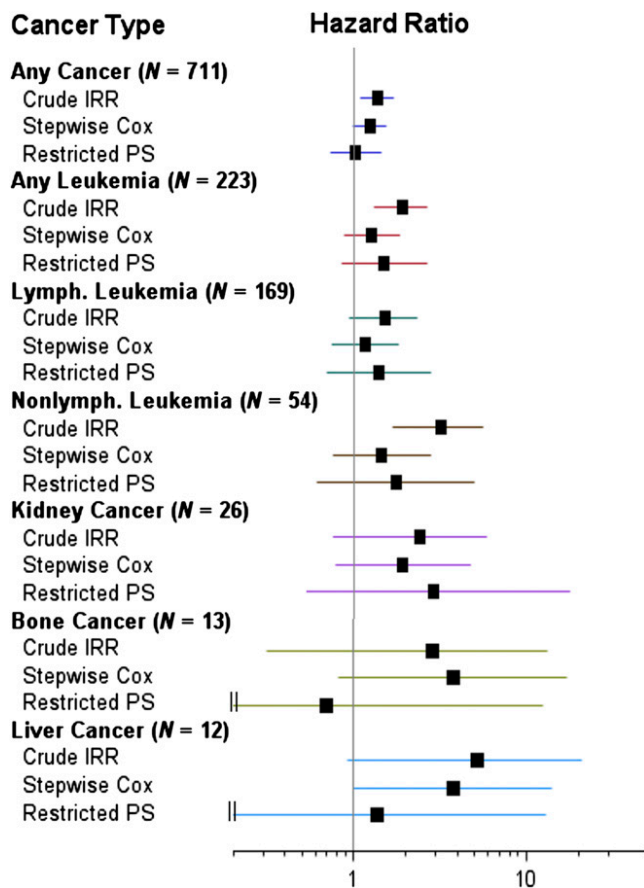
FIGURE 3

Hazard ratios and 95% CIs for phototherapy by type of cancer and model. Stepwise Cox, Cox proportional hazard model on entire cohort; Restricted PS, propensity score model restricted to infants with bilirubin levels at which phototherapy was often used.

The key question is therefore whether the association is entirely due to confounding, that is, to one or more factors that cause both phototherapy and cancer (particularly leukemia). One key confounder is Down syndrome. In both the California Late Impact of Phototherapy Study[20] and the current study, Down syndrome was associated not only with a markedly increased risk of leukemia but also a fivefold increase in the use of phototherapy. As reported in previous studies, other chromosomal and congenital anomalies[26] and low 5-minute Apgar score[27] were also associated with certain types of cancer and were associated with higher phototherapy rates. Controlling for these confounding variables attenuated

or eliminated the associations but widened CIs.

The possible confounding effect of high bilirubin levels is worth particular attention, because such levels have not been available in previous studies of childhood cancer. We have previously shown[3,23] that quantifying TSB levels in 1-mg/dL categories in relation to AAP treatment guidelines effectively controls confounding by indication. Thus our primary prespecified analysis was restricted to infants who had TSB levels from −3 mg/dL to +4.9 mg/dL from AAP treatment thresholds, which made them potential (but not almost certain) candidates for phototherapy, a group that most closely approximates subjects who would have been eligible

for inclusion in a randomized trial of phototherapy. Restricted propensity analyses that controlled for TSB in this way found that associations between phototherapy and cancer were attenuated and not statistically significant. We obtained similar results with inclusive propensity models and with stepwise Cox models, suggesting the results were not dependent on the analytic strategy.

One limitation of this observational study is that we cannot control for unmeasured confounding variables. Breastfeeding, which was not available as a covariate for this study, is associated with higher bilirubin levels[21,28,29] and lower leukemia risk,[30] However, because breastfeeding affects phototherapy use largely by affecting TSB levels, controlling for TSB should control for most confounding by breastfeeding.

A second limitation is lack of data on phototherapy dosage. We crudely estimated phototherapy dosage from the number of admissions at which it was given and found an increase in myelogenous leukemia at the highest dose. Although this is the only positive adjusted analysis of many we did and included only 2 exposed cases, myelogenous leukemia was the outcome about which we had the greatest a priori concerns, so this result cannot be easily dismissed. Other adjusted results that were not statistically significant had upper limits of CI for HRs of 2 or 3 for all leukemia and lymphocytic leukemia and were wider for less common cancers. However, even if the HRs for any phototherapy were at the top of the 95% CIs reported in this study, absolute risk of cancer from phototherapy would be low, at least in childhood (<1/1000 over 10 years).

Is that potential risk worth taking? Phototherapy is often given at TSB levels at which the number needed to treat to prevent 1 infant from

reaching exchange levels is in the hundreds or thousands.[3] Recent data suggest that unless exchange transfusion thresholds are exceeded by at least 10 mg/dL, there is little or no increased risk of cerebral palsy[7] or hearing loss.[8] Thus, even the low upper limit of risk of cancer may exceed the likely benefits of treatment in many infants. The likelihood of harms exceeding benefits is greatest in children with Down syndrome, whose much higher baseline risk of leukemia might lead cautious clinicians to increase the treatment threshold for initiation of phototherapy in these infants, despite the fact that the association between phototherapy and cancer has not yet been proven to be causal.

CONCLUSIONS

Although we confirmed a crude association between phototherapy and childhood cancer, particularly nonlymphocytic leukemia, associations were diminished and no longer statistically significant after we controlled for confounding variables. Nonetheless, consistent crude associations, clinically relevant upper limits of adjusted 95% CIs, and the statistically significant adjusted association between multiple phototherapy admissions and myelogenous leukemia suggest that avoiding unnecessary phototherapy would be prudent, especially in children with Down syndrome.

ABBREVIATIONS

AAP: American Academy of Pediatrics
CI: confidence interval
HR: hazard ratio
ICD-9: International Classification of Diseases, Ninth Revision
IRR: incidence rate ratio
KPNC: Kaiser Permanente Northern California
OR: odds ratio
TSB: total serum bilirubin

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