Neonatal Phototherapy and Infantile Cancer

Andrea C. Wickremasinghe, MD,[a,b] Michael W. Kuzniewicz, MD, MPH,[c,d] Barbara A. Grimes, PhD,[b] Charles E. McCulloch, PhD,[b] Thomas B. Newman, MD, MPH[b,c,d]

abstract

OBJECTIVE: To determine whether neonatal phototherapy is associated with cancer in the first year after birth.

METHODS: We analyzed a data set from the California Office of Statewide Health Planning and Development that was created by linking birth certificates, death certificates, and hospital discharge abstracts up to age 1 year. Subjects were 5 144 849 infants born in California hospitals at ≥35 weeks' gestation from 1998 to 2007. We used International Classification of Diseases, Ninth Revision codes to identify phototherapy at <15 days and discharge diagnoses of cancer at 61 to 365 days. We adjusted for potential confounding variables by using traditional and propensity-adjusted logistic regression models.

RESULTS: Cancer was diagnosed in 58/178 017 infants with diagnosis codes for phototherapy and 1042/4 966 832 infants without such codes (32.6/100 000 vs 21.0/100 000; relative risk 1.6; 95% confidence interval [CI], 1.2–2.0, $P = .002$). In propensity-adjusted analyses, associations were seen between phototherapy and overall cancer (adjusted odds ratio [aOR] 1.4; 95% CI, 1.1–1.9), myeloid leukemia (aOR 2.6; 95% CI, 1.3–5.0), and kidney cancer (aOR 2.5; 95% CI, 1.2–5.1). The marginal propensity-adjusted absolute risk increase for cancer after phototherapy in the total population was 9.4/100 000 (number needed to harm of 10 638). Because of the higher baseline risk of cancer in infants with Down syndrome, the number needed to harm was 1285.

CONCLUSIONS: Phototherapy may slightly increase the risk of cancer in infancy, although the absolute risk increase is small. This risk should be considered when making phototherapy treatment decisions, especially for infants with bilirubin levels below current treatment guidelines.

FREE

[a]*Department of Pediatrics, Kaiser Permanente Northern California, Santa Clara, California;* [b]*Department of Epidemiology & Biostatistics, and* [c]*Department of Pediatrics, University of California, San Francisco, California; and* [d]*Division of Research, Kaiser Permanente Northern California, Oakland, California*

Dr Wickremasinghe assisted with study design, obtained funding, obtained data, carried out the initial analyses, and drafted the initial manuscript; Dr Kuzniewicz assisted with study design and reviewed and revised the manuscript; Dr Grimes provided statistical consultation and reviewed and revised the manuscript; Dr McCulloch assisted with study design, provided statistical consultation, and reviewed and revised the manuscript; Dr Newman conceptualized and designed the study, assisted with obtaining funding and statistical analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-1353

Accepted for publication Mar 25, 2016

Address correspondence to Andrea C. Wickremasinghe, MD, Department 302—Neonatology, Kaiser Permanente Santa Clara Medical Center, 700 Lawrence Expy, Santa Clara, CA 95051. E-mail: andrea.wickremasinghe@kp.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

WHAT'S KNOWN ON THIS SUBJECT: Phototherapy is commonly used to treat neonatal jaundice. It is generally thought to be safe. However, a small number of studies have suggested an association between neonatal phototherapy and cancer.

WHAT THIS STUDY ADDS: In this study of ~5 million California births, phototherapy was associated with a small but statistically significant increased risk of some infantile cancers, specifically myeloid leukemia and kidney cancer, with ~1 additional cancer case per 10 638 treated infants.

To cite: Wickremasinghe AC, Kuzniewicz MW, Grimes BA, et al. Neonatal Phototherapy and Infantile Cancer. *Pediatrics.* 2016;137(6):e20151353

Phototherapy is commonly used to treat neonatal jaundice. The use of phototherapy has been increasing[1,2]; a recent study of term and near-term infants enrolled in a single health plan in California showed that up to 15.9% received this treatment.[3] Many clinicians initiate phototherapy at levels lower than those recommended by the American Academy of Pediatrics.[2,4] The rise in phototherapy use may be a result of increased identification of neonates with hyperbilirubinemia through universal screening protocols,[2] fear of kernicterus,[5] and general belief that phototherapy is safe.[4]

Although phototherapy is thought to pose minimal risk to infants with unconjugated hyperbilirubinemia,[4,6] 2 large epidemiologic studies have found phototherapy to be associated with subsequent cancer (overall leukemia and acute myelogenous leukemia).[7,8] These associations have not been consistent; some studies have been reassuring,[9,10] but none have been large enough to be conclusive. The potential for phototherapy to increase the incidence of cancer is supported by data from in vitro and in vivo studies.[11–22]

It is important to determine whether phototherapy contributes to early childhood cancer to determine the optimal management of infants with neonatal hyperbilirubinemia. In this study, we used population-based data to investigate the association between phototherapy and cancer in the first year after birth.

METHODS

Study Design and Subjects

This study is an analysis of a historical cohort of infants born in California between January 1, 1998 and December 31, 2007. We used the linked Vital Statistics/Patient Discharge Dataset (VS/PDD) for our analyses. The VS/PDD was created for the California Office of Statewide Health Planning and Development by using probabilistic linkage of data from birth certificates, death certificates, and hospital discharge abstracts for mothers and their newborn infants up to 1 year of age.[23] The VS/PDD includes all California births except those of infants born at home or in military hospitals. For our analyses, we excluded infants born at <35 weeks' gestation and infants who died within 60 days of birth.

This study was approved by the institutional review boards for the protection of human subjects at the California Health and Human Services Agency, California Department of Public Health, and the University of California, San Francisco.

Predictor Variables

The primary predictor variable was receipt of phototherapy during a hospitalization that began within the first 2 weeks after birth. We ascertained phototherapy use by abstracting International Classification of Diseases, Ninth Revision (ICD-9)[24] procedure codes for phototherapy (99.82, 99.83).

Covariates abstracted from the birth certificates included gender, birth weight, gestational age, twin birth, birth by cesarean delivery, payer source, year of birth, and maternal and paternal demographic variables (race, Hispanic ethnicity, age, and education). Covariates abstracted from discharge diagnosis ICD-9 codes included jaundice (774.0–774.4, 774.5, 774.6, 782.4), Down syndrome (758.0), other chromosomal anomalies (758.1–758.9), and nonchromosomal congenital anomalies (740.0–743.64, 743.66–749.25, 750.1–757.32, 757.39–757.9, 759.0–759.9); only congenital anomalies diagnosed during the birth hospitalization were included.

Data were missing for several of our covariates, most commonly payer source (missing in 12.1%), paternal education (9.4%), gestational age (7.1%), paternal age (7.1%), and paternal race (6.9%). We imputed missing values by using single regression imputation because of the large size of the data set. To estimate the effect of the missing data on the precision of our results, we performed multiple imputation (5 imputations) on a subset that included all cancer cases and a 1% sample of the remainder of the cohort. We included subjects with missing gestational age if their imputed gestational age (based on multiple variables including birth weight, parental race, parental age, mode of delivery, and twin status) was ≥35 weeks.

Outcome Variables

The primary outcome was a hospital discharge diagnosis of cancer (ICD-9 codes 140.0–209.79, 230.0–234.9) in the first year after birth. We excluded cancers diagnosed at ≤60 days to reduce the likelihood of finding an association through reverse causation. In addition, it seemed less plausible that phototherapy would cause cancer in ≤60 days. We grouped cancer diagnosis ICD-9 codes by site: myeloid leukemia (205.0–205.92), lymphoid leukemia (204.0–204.92), brain or nervous system (191.0–192.9), kidney (189.0–189.9), liver (155.0–156.9), soft tissue (171.0–171.9), and other (remaining codes). If an infant had >1 type of cancer diagnosis, all were captured.

Statistical Analysis

We used Stata 13 (Stata Corp, College Station, TX) statistical software for all analyses. We performed bivariate analyses comparing infants with and without cancer diagnoses by using χ^2 tests for categorical variables and t tests for continuous variables.

We computed risk ratios (RRs) and risk differences for phototherapy and each of the cancer outcomes by using the Agresti-Caffo method[25] to

compare risk differences. Because the exposure (phototherapy) is much more common than the outcome (various types of cancer), creating a model for exposure allowed control for many more potential confounding variables than traditional analyses that create a model for the outcome. We therefore created a propensity score for phototherapy with the following covariates: gender, birth weight, gestational age, large for gestational age, twin birth, birth by cesarean delivery, payer source, year of birth, maternal race, paternal race, maternal Hispanic ethnicity, maternal age, paternal age, maternal education, paternal education, Down syndrome, other chromosomal anomalies, and nonchromosomal congenital anomalies. The propensity score had an area under the receiver operating characteristic curve of 0.67. We then used logistic regression to evaluate the association between phototherapy and cancer, adjusted for the propensity to receive phototherapy. In the propensity-adjusted analyses, the predictor variables were only phototherapy and propensity to receive phototherapy (in categories). We calculated unadjusted and marginal propensity-adjusted risk differences and 95% confidence intervals (CIs) of the risk differences; we calculated marginal risk differences because they estimate effect in the entire population (ie, if all versus no infants were treated with phototherapy), whereas other risk differences depend on baseline risk (ie, the values of other covariates).[26] We calculated numbers needed to harm by taking the reciprocal of the risk differences. To complement propensity-adjusted models, we also analyzed the data in traditional multivariable logistic models adjusted for gender, birth weight, gestational age, Down syndrome, maternal race, and year of birth. To ensure that imputation did not affect our results, we performed a complete case analysis.

TABLE 1 Description of Cohort (n = 5 144 861), by Diagnosis of Cancer

	Cancer Diagnosis		P
	Yes (n = 1100)	No (n = 5 143 749)	
Male, %	55.2	51	.005
Gestation in wk, mean (SD)	39.5 (1.7)	39.5 (1.6)	.65
Birth wt in g, mean (SD)	3411 (511)	3385 (503)	.09
Large for gestational age, %[a]	10.9	9.9	.28
Twin, %	2.4	2.2	.74
Down syndrome, %	1.6	0.2	<.001
Other chromosomal anomalies, %	0.6	0.1	<.001
Congenital anomalies, %	7.7	4.1	<.001
Maternal race, %			.1
White	83	80.2	
Black	5	5.8	
Asian	10.2	11.4	
Other	1.9	2.6	
Maternal Hispanic ethnicity, %	50.6	47.5	.04
Paternal race, %			.36
White	82.4	80.2	
Black	5.8	6.7	
Asian	9.4	10.6	
Other	2.4	2.6	
Maternal age in y, mean (SD)	28.2 (6.4)	27.9 (6.3)	.08
Paternal age in y, mean (SD)	30.9 (7)	30.8 (7.1)	.58
Maternal education, %			.78
Did not complete high school	31.4	29.8	
Completed high school, no college	26.3	27.4	
Completed some college	20.2	20	
Completed 4 y of college	12.6	13.1	
Completed >4 y of college	9.5	9.8	
Paternal education, %			.7
Did not complete high school	30.4	28.5	
Completed high school, no college	29.2	29.2	
Completed some college	16.7	17.9	
Completed 4 y of college	12.8	13.2	
Completed >4 y of college	11	11.1	
Cesarean delivery, %	29.5	26.2	.02
Payer, %			.07
Private insurance	50.6	51.5	
Medi-Cal	46.7	44.6	
Other	2.7	4	

[a] Large for gestational age is defined as >90th percentile (in this data set).

Because Down syndrome is such a strong risk factor for cancer,[27] we estimated the marginal propensity-adjusted risk difference and 95% CI for cancer after phototherapy in infants with and without Down syndrome separately. For this analysis, we created a propensity score without the Down syndrome variable.

RESULTS

Our cohort consisted of 5 144 849 infants born at ≥35 weeks' gestation who were alive >60 days after birth. A cancer diagnosis was present in 1100 of the infants, yielding an overall population incidence of 21.4/100 000. Table 1 provides a description of the cohort by cancer diagnosis status. The most common cancers were leukemia (23%), brain or nervous system cancer (16%), and eye or orbit cancer (9%).

Jaundice diagnoses were recorded in 13.9% of infants and phototherapy codes in 3.5% of the cohort. Phototherapy use increased over time, from 2.9% in 1998 to 4.4% in 2007 (P < .001). Of subjects who received phototherapy, 85% had a jaundice diagnosis. Jaundice itself was associated with an increased

risk of cancer, controlling for phototherapy (RR 1.3; 95% CI, 1.1–1.5).

In unadjusted analyses, subjects who received phototherapy were at higher risk of overall cancer (RR 1.6; 95% CI, 1.2–2.0), myeloid leukemia (RR 2.7; 95% CI, 1.4–5.2), kidney cancer (RR 2.7; 95% CI, 1.3–5.6), and other cancer (RR 1.7; 95% CI, 1.1–2.5), although the risk differences were small (Tables 2 and 3). The associations between phototherapy and overall cancer, myeloid leukemia, kidney cancer, and other cancer persisted in propensity-adjusted models (Table 3). Propensity-adjusted models, traditional multivariable-adjusted models, and models with and without multiple imputation gave similar results. In a complete case analysis (n = 3 717 503), we found similar propensity-adjusted associations between phototherapy and overall cancer (odds ratio [OR] 1.5; 95% CI, 1.1–2.1), myeloid leukemia (OR 2.2; 95% CI, 1.0–4.9), kidney cancer (OR 3.4; 95% CI, 1.6–7.3), and other cancer (OR 1.7; 95% CI, 1.1–2.7). After adjustment for jaundice alone, the association between phototherapy and myeloid leukemia was similar (OR 2.6; 95% CI, 1.2–5.6), the associations between phototherapy and overall cancer (OR 1.3; 95% CI, 1.0–1.8) and other cancer (OR 1.5; 95% CI, 1.0–2.4) were slightly diminished, and the association between phototherapy and kidney cancer (OR 1.6; 95% CI, 0.7–3.5) was diminished further. The marginal propensity-adjusted absolute risk increase for cancer after phototherapy in the total population was 9.4/100 000 (95% CI, 1.4/100 000–17.4/100 000), with a number needed to harm of 10 638.

Down syndrome was diagnosed in 7812 subjects (0.2% of the cohort). In the subgroup of infants with Down syndrome, 19% received phototherapy. Cancer was diagnosed in 18 infants with Down syndrome (lymphoid leukemia in 4, myeloid leukemia in 10, other leukemia in 2, brain or nervous system cancer in 1, and other cancer in 1). The marginal propensity-adjusted absolute risk increase for cancer after phototherapy was much higher for infants with Down syndrome (77.8/100 000; 95% CI, -1.2/100 000–156.8/100 000, number needed to harm of 1285) than for infants without Down syndrome (8.1/100 000, 95% CI 0.4/100 000–15.8/100 000, number needed to harm of 12 346). This difference was caused by the higher baseline risk of cancer in infants with Down syndrome; the propensity-adjusted ORs for cancer after

TABLE 2 Incidence of Cancer by Whether Infants Received Phototherapy, by Cancer Site

	Phototherapy (n = 178 017)		No Phototherapy (n = 4 966 832)		Unadjusted Risk Difference (per 100 000)	95% CI (per 100 000)	P[a]
	N[b]	Incidence (per 100 000)	N[b]	Incidence (per 100 000)			
All cancer	58	32.6	1042	21.0	11.6	3.6 to 20.7	.002
Leukemia	16	9.0	242	4.9	4.1	0.1 to 9.2	.025
Lymphoid leukemia	6	3.4	133	2.7	0.7	−1.7 to 4.2	.49
Myeloid leukemia	10	5.6	103	2.1	3.5	0.4 to 7.8	.006
Brain or nervous system cancer	7	3.9	176	3.5	0.4	−2.2 to 4.1	.69
Eye or orbit cancer	4	2.3	103	2.1	0.2	−1.8 to 3.2	.79
Kidney cancer	8	4.5	82	1.7	2.8	0.1 to 6.7	.013
Liver cancer	2	1.1	81	1.6	−0.5	−1.9 to 2.0	1.0
Soft tissue cancer	1	0.6	69	1.4	−0.8	−1.9 to 1.3	.52
Other cancer	26	14.6	426	8.6	6.0	0.8 to 12.4	.013

[a] Fisher's exact test used.
[b] Some subjects had >1 type of cancer.

TABLE 3 RRs and Propensity-Adjusted ORs for the Association Between Phototherapy and Cancer, by Cancer Site

	N[a]	Unadjusted Analyses			Propensity-Adjusted Analyses[b]		
		RR	95% CI	P[c]	OR	95% CI	P
All cancer	1100	1.6	1.2 to 2.0	.002	1.4	1.1 to 1.9	.007
Leukemia	258	1.8	1.1 to 3.1	.03	1.8	1.1 to 3.1	.02
Lymphoid leukemia	139	1.3	0.6 to 2.9	.49	1.3	0.6 to 2.9	.55
Myeloid leukemia	113	2.7	1.4 to 5.2	.006	2.6	1.3 to 5.0	.005
Brain or nervous system cancer	183	1.1	0.5 to 2.4	.69	1.0	0.5 to 2.1	.97
Eye or orbit cancer	107	1.1	0.4 to 2.9	.79	1.0	0.4 to 2.7	.96
Kidney cancer	90	2.7	1.3 to 5.6	.01	2.5	1.2 to 5.1	.02
Liver cancer	83	0.7	0.2 to 2.8	1.0	0.6	0.2 to 2.5	.5
Soft tissue cancer	70	0.4	0.1 to 2.9	.52	0.4	0.1 to 2.7	.33
Other cancer	452	1.7	1.1 to 2.5	.01	1.6	1.1 to 2.4	.02

[a] Some subjects had >1 type of cancer.
[b] Propensity-adjusted model included a propensity score for phototherapy that included the following variables: gender, birth wt, gestational age, large for gestational age, twin birth, birth by cesarean delivery, payer source, year of birth, maternal race, paternal race, maternal Hispanic ethnicity, maternal age, paternal age, maternal education, paternal education, Down syndrome, other chromosomal anomalies, and nonchromosomal congenital anomalies. The propensity score had an area under the receiver operating characteristic curve of 0.67.
[c] Fisher's exact test used.

phototherapy were similar: 1.2 for infants with Down syndrome and 1.4 for infants without Down syndrome (*P* for interaction = .79).

DISCUSSION

In this study, we found that neonatal phototherapy was associated with an increased risk of cancer in the first year after birth; these associations persisted in adjusted analyses. Specifically, we found associations between phototherapy and overall cancer (adjusted odds ratio [aOR] 1.4), myeloid leukemia (aOR 2.6), kidney cancer (aOR 2.5), and other cancer (aOR 1.6). Based on our findings, 10 638 infants would need to be treated with neonatal phototherapy to cause 1 excess case of infantile cancer.

With epidemiologic studies, it is important to consider whether associations found are biologically plausible. The potential for phototherapy to increase the incidence of cancer is supported by evidence dating from the 1970s that blue light is mutagenic in vitro.[11] Additionally, in vivo experiments on human newborns have demonstrated DNA damage, alterations in cytokine levels, and evidence of oxidative stress after treatment with phototherapy.[12–22] This is concerning because all these conditions have been implicated in the pathogenesis of cancer.[28,29] Although the clinical importance of these alterations remains to be elucidated, they present a potential mechanism whereby phototherapy could be related to childhood cancer.

The association between phototherapy and leukemia reported here has been previously suggested in other large epidemiologic studies. A population-based case–control study from the state of Washington found neonatal jaundice to be associated with an increased risk of leukemia (OR 1.5; 95% CI, 1.1–2.1).[7] In a subgroup analysis, the risk of leukemia was higher in jaundiced infants who received phototherapy (OR 2.2; 95% CI, 1.0–4.9).[7] A Swedish case–control study found increased odds of myeloid leukemia in infants with physiologic jaundice (OR 2.5; 95% CI, 1.2–5), which again was more pronounced in those treated with phototherapy (OR 7.5; 95% CI, 1.8–31.9).[8] As in the current study, the Swedish group did not find an association between phototherapy and lymphoid leukemia (OR 1.0; 95% CI, 0.5–1.8).[30]

Two other studies did not find an association between phototherapy and cancer. A case–control study from the United Kingdom with 143 leukemia cases found no statistically significant association between phototherapy and leukemia (OR 0.5; 95% CI, 0.1–2.3); in this study, none of the 15 subjects with myeloid leukemia received phototherapy (OR 0; 95% CI, 0–11.7).[10] A Danish study of 55 120 children with neonatal hyperbilirubinemia found no association between hyperbilirubinemia and overall cancer (standardized incidence ratio [SIR] 1.0; 95% CI, 0.8–1.3) or any subtype, including leukemia (SIR 1.2; 95% CI, 0.8–1.7) and kidney cancer (SIR 1.0; 95% CI, 0.4–2.2).[9] The authors of that study estimated that 85% to 90% of the children with hyperbilirubinemia received phototherapy, but they were unable to specifically evaluate the association between phototherapy and cancer.

In this study, we also found an association between phototherapy and other cancer. The "other cancer" group included an excess of bone cancer, which is extremely rare in infancy, suggesting that this group consists, at least in part, of metastases and misclassified cancers. Nonetheless, we found a persistent association between phototherapy and these other cancers.

Our study has the advantage of a large cohort, with >5 million infants and 1100 cancer cases. The incidence of cancer in our study is similar to what is reported from US Cancer Registries,[31] which suggests that our ascertainment of cancer cases was reasonably complete.

Because we used a large statewide data set, this study has a few limitations. We were unable to adjust for potential confounding variables not included in the data set. As an example, because serum bilirubin levels were not available, we cannot exclude the possibility that the association between phototherapy and cancer could be caused by elevated bilirubin levels (not captured by a discharge diagnosis of jaundice). The association between phototherapy and cancer persisted in analyses adjusted for a discharge diagnosis of jaundice, although a diagnosis of jaundice is admittedly a crude indicator of hyperbilirubinemia.

Because data on phototherapy intensity and duration were not available, we could not investigate the effect of phototherapy dosage. We did not have data on home phototherapy; we hypothesize that misclassification of subjects who received home phototherapy as unexposed would attenuate the observed association between phototherapy and cancer. Our ascertainment of phototherapy and of cancer diagnoses was probably incomplete, but it is unlikely that the completeness or accuracy of cancer coding differed between those who did and did not receive phototherapy or that the accuracy of phototherapy coding differed depending on subsequent risk of cancer. Such nondifferential misclassification, if present, would have biased our ORs toward 1. Also, the data set we used is limited to the first year after birth.

In a companion study, Newman et al[3] looked at the association between neonatal phototherapy and childhood cancer in a cohort of almost 500 000 children born over a

17-year period in Kaiser Permanente Northern California hospitals. In that study, phototherapy was associated with an increased risk of overall cancer and nonlymphocytic leukemia in unadjusted models, but these associations were no longer statistically significant after researchers adjusted for potential confounders. These results could reflect the ability to adjust for additional potential confounders that were not available in our data set (eg, bilirubin levels). However, the 95% CI reported in that study did not exclude adjusted differences of the magnitude reported here. It is also possible that phototherapy causes only infantile or early childhood cancer; the Newman et al finding of increased early (<3 years) nonlymphocytic leukemia could support this hypothesis.

Although we found an increased risk of cancer in infants who received phototherapy, the absolute risk increase among those who received phototherapy was low. However, for infants with Down syndrome, the absolute risk increase was almost 10 times higher because of their higher baseline risk for cancer.

The possible increase in cancer risk from using phototherapy must be balanced against its benefit for lowering bilirubin levels. Phototherapy use has decreased rates of exchange transfusions,[32] a procedure estimated to have 5% morbidity and up to 1.9% mortality risks.[33] However, the number of infants with bilirubin levels near phototherapy treatment thresholds who need to be treated to prevent 1 from reaching exchange transfusion thresholds varies widely (from 10 to >3000, based on gender, gestational age, and age).[34] Additionally, having bilirubin levels at or just above exchange transfusion thresholds is typically benign; it is not until bilirubin levels are >5 to 10 mg/dL above exchange transfusion thresholds that the risks of cerebral palsy and sensorineural hearing loss increase significantly.[35–40] Therefore, especially in infants with bilirubin levels below recommended treatment thresholds and in infants with Down syndrome, the risks of phototherapy may exceed the benefits.

CONCLUSIONS

Phototherapy is a valuable treatment for infants with neonatal hyperbilirubinemia. Our results support the need for health care providers to consider phototherapy as they do most other treatments (ie, as having both benefits and potential risks) and to limit the use of phototherapy to infants for whom the benefit/risk balance is most likely to be favorable.

ACKNOWLEDGMENTS

The authors thank Dr Beate Danielsen for her assistance on this project. Statistical analysis for this project was partially supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI grant UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

ABBREVIATIONS

aOR: adjusted odds ratio
CI: confidence interval
ICD-9: International Classification of Diseases, Ninth Revision
OR: odds ratio
RR: risk ratio
SIR: standardized incidence ratio
VS/PDD: Vital Statistics/Patient Discharge Dataset

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Gerber Foundation Novice Research Award and American Academy of Pediatrics Marshall Klaus Perinatal Research Award to A.C.W.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Companions to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2015-1354 and www.pediatrics.org/cgi/doi/10.1542/peds.2016-0983.

REFERENCES

1. Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988–2005. *Pediatrics*. 2009;123(2):524–532
2. Kuzniewicz MW, Escobar GJ, Newman TB. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. *Pediatrics*. 2009;124(4):1031–1039
3. Newman TB, Wickremasinghe AC, Walsh EM, Grimes BA, McCulloch CE, Kuzniewicz MW. Retrospective cohort study of phototherapy and childhood cancer in northern California. *Pediatrics*. 2016;137(6):e20151334
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316
5. Davidson L, Thilo EH. How to make kernicterus a "never event." *NeoReviews*. 2003;4(11):e308–e314

6. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med*. 2008;358(9):920–928

7. Podvin D, Kuehn CM, Mueller BA, Williams M. Maternal and birth characteristics in relation to childhood leukaemia. *Paediatr Perinat Epidemiol*. 2006;20(4):312–322

8. Cnattingius S, Zack M, Ekbom A, Gunnarskog J, Linet M, Adami HO. Prenatal and neonatal risk factors for childhood myeloid leukemia. *Cancer Epidemiol Biomarkers Prev*. 1995;4(5):441–445

9. Olsen JH, Hertz H, Kjaer SK, Bautz A, Mellemkjaer L, Boice JD Jr. Childhood leukemia following phototherapy for neonatal hyperbilirubinemia (Denmark). *Cancer Causes Control*. 1996;7(4):411–414

10. Roman E, Ansell P, Bull D. Leukaemia and non-Hodgkin's lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? *Br J Cancer*. 1997;76(3):406–415

11. Speck WT, Rosenkranz HS. Phototherapy for neonatal hyperbilirubinemia—a potential environmental health hazard to newborn infants: a review. *Environ Mutagen*. 1979;1(4):321–336

12. Tsai FJ, Tsai CH, Peng CT, Wang TR. Sister chromatid exchange in Chinese newborn infants treated with phototherapy for more than five days. *Zhonghua Minguo Xiao Er Ke Yi Xue Hui*. 1998;39(5):327–329

13. Galla A, Kitsiou-Tzeli S, Gourgiotis D, et al. Sister chromatid exchanges in peripheral lymphocytes in newborns treated with phototherapy and vitamin E. *Acta Paediatr*. 1992;81(10):820–823

14. Karadag A, Yesilyurt A, Unal S, et al. A chromosomal-effect study of intensive phototherapy versus conventional phototherapy in newborns with jaundice. *Mutat Res*. 2009;676(1-2):17–20

15. Tatli MM, Minnet C, Kocyigit A, Karadag A. Phototherapy increases DNA damage in lymphocytes of hyperbilirubinemic neonates. *Mutat Res*. 2008;654(1):93–95

16. Aycicek A, Erel O. Total oxidant/antioxidant status in jaundiced newborns before and after phototherapy. *J Pediatr (Rio J)*. 2007;83(4):319–322

17. Aycicek A, Kocyigit A, Erel O, Senturk H. Phototherapy causes DNA damage in peripheral mononuclear leukocytes in term infants. *J Pediatr (Rio J)*. 2008;84(2):141–146

18. Gathwala G, Sharma S. Oxidative stress, phototherapy and the neonate. *Indian J Pediatr*. 2000;67(11):805–808

19. Gathwala G, Sharma S. Phototherapy induces oxidative stress in premature neonates. *Indian J Gastroenterol*. 2002;21(4):153–154

20. Sirota L, Straussberg R, Gurary N, Aloni D, Bessler H. Phototherapy for neonatal hyperbilirubinemia affects cytokine production by peripheral blood mononuclear cells. *Eur J Pediatr*. 1999;158(11):910–913

21. Kurt A, Aygun AD, Kurt AN, Godekmerdan A, Akarsu S, Yilmaz E. Use of phototherapy for neonatal hyperbilirubinemia affects cytokine production and lymphocyte subsets. *Neonatology*. 2009;95(3):262–266

22. Ramy N, Ghany EA, Alsharany W, et al Jaundice, phototherapy and DNA damage in full-term neonates. *J Perinatol*. 2016;36(2):132–136

23. Herrchen B, Gould JB, Nesbitt TS. Vital statistics linked birth/infant death and hospital discharge record linkage for epidemiological studies. *Comput Biomed Res*. 1997;30(4):290–305

24. Practice Management Information Corporation. *ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification, Fifth Edition, Color Coded, 2000. Hospital Edition*. Los Angeles, CA: Practice Management Information Corporation; 1999

25. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. *Am Stat*. 2000;54(4):280–288

26. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. *Stata J*. 2012;12(2):308–331

27. Fong CT, Brodeur GM. Down's syndrome and leukemia: epidemiology, genetics, cytogenetics and mechanisms of leukemogenesis. *Cancer Genet Cytogenet*. 1987;28(1):55–76

28. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer*. 2004;4(1):11–22

29. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact*. 2006;160(1):1–40

30. Cnattingius S, Zack MM, Ekbom A, et al. Prenatal and neonatal risk factors for childhood lymphatic leukemia. *J Natl Cancer Inst*. 1995;87(12):908–914

31. US Cancer Statistics. 1999–2011 Incidence. WONDER online database. 2014. Available at: http://wonder.cdc.gov/cancer-v2011.html. Accessed February 5, 2015

32. Steiner LA, Bizzarro MJ, Ehrenkranz RA, Gallagher PG. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. *Pediatrics*. 2007;120(1):27–32

33. Ip S, Chung M, Kulig J, et al; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatrics*. 2004;114(1). Available at: www.pediatrics.org/cgi/content/full/114/1/e130

34. Newman TB, Kuzniewicz MW, Liljestrand P, Wi S, McCulloch C, Escobar GJ. Numbers needed to treat with phototherapy according to American Academy of Pediatrics guidelines. *Pediatrics*. 2009;123(5):1352–1359

35. Wu YW, Kuzniewicz MW, Wickremasinghe AC, et al. Risk for cerebral palsy in infants with total serum bilirubin levels at or above the exchange transfusion threshold: a population-based study. *JAMA Pediatr*. 2015;169(3):239–246

36. Wickremasinghe AC, Risley RJ, Kuzniewicz MW, et al. Risk of sensorineural hearing loss and bilirubin exchange transfusion thresholds. *Pediatrics*. 2015;136(3):505–512

37. Kuzniewicz MW, Wickremasinghe AC, Wu YW, et al. Incidence, etiology,

and outcomes of hazardous hyperbilirubinemia in newborns. *Pediatrics*. 2014;134(3):504–509

38. Ebbesen F, Bjerre JV, Vandborg PK. Relation between serum bilirubin levels ≥450 μmol/L and bilirubin encephalopathy; a Danish population-based study. *Acta Paediatr*. 2012;101(4):384–389
39. Vandborg PK, Hansen BM, Greisen G, Jepsen M, Ebbesen F. Follow-up of neonates with total serum bilirubin levels ≥25 mg/dL: a Danish population-based study. *Pediatrics*. 2012;130(1):61–66
40. Vandborg PK, Hansen BM, Greisen G, Mathiasen R, Kasper F, Ebbesen F. Follow-up of extreme neonatal hyperbilirubinaemia in 5- to 10-year-old children: a Danish population-based study. *Dev Med Child Neurol*. 2015;57(4):378–384

Neonatal Phototherapy and Infantile Cancer

Andrea C. Wickremasinghe, Michael W. Kuzniewicz, Barbara A. Grimes, Charles E. McCulloch and Thomas B. Newman

Pediatrics 2016;137;
DOI: 10.1542/peds.2015-1353 originally published online May 23, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neonatal Phototherapy and Infantile Cancer

Andrea C. Wickremasinghe, Michael W. Kuzniewicz, Barbara A. Grimes, Charles E. McCulloch and Thomas B. Newman

Pediatrics 2016;137;
DOI: 10.1542/peds.2015-1353 originally published online May 23, 2016;