Update on Phototherapy and Childhood Cancer in a Northern California Cohort

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abstract

OBJECTIVES: We aimed to reassess the relationship between phototherapy and cancer in an extended version of a previous cohort and to replicate a report from Quebec of increased cancer risk after phototherapy beginning at age 4 years.

METHODS: This cohort study included 139 100 children born at ≥35 weeks' gestation from 1995 to 2017, followed through March 16, 2019, in Kaiser Permanente Northern California hospitals who had a qualifying bilirubin level from −3 mg/dL to +4.9 mg/dL from the American Academy of Pediatrics phototherapy threshold; an additional 40 780 children and 5 years of follow-up from our previous report. The exposure was inpatient phototherapy (yes or no), and the outcomes were various types of childhood cancer. We used Cox proportional hazard models, controlling for propensity-score quintiles, and allowed for time-dependent exposure effects to assess for the risk of cancer after a latent period.

RESULTS: Over a mean (SD) follow-up of 8.2 (5.7) years, the crude incidence of cancer per 100 000 person-years was 25.1 among those exposed to phototherapy and 19.2 among those not exposed (233 cases of cancer). After propensity adjustment, phototherapy was not associated with any cancer (hazard ratio [HR]: 1.13, 95% confidence interval [CI]: 0.83–1.54), hematopoietic cancer (HR: 1.17, 95% CI: 0.74–1.83), or solid tumors (HR: 1.01, 95% CI: 0.65–1.58). We also found no association with cancer diagnoses at age ≥4 years.

CONCLUSIONS: We did not confirm previous, concerning associations between phototherapy and adjusted risk of any cancer, nonlymphocytic leukemia, or brain and/or central nervous systems tumors in later childhood.

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WHAT'S KNOWN ON THIS SUBJECT: There is conflicting evidence as to whether phototherapy given to jaundiced newborns may have a carcinogenic effect. A recent study from Quebec suggested phototherapy could increase the risk of solid tumors but only after a latent period of several years.

WHAT THIS STUDY ADDS: In an extended version of a large Northern California cohort, we did not replicate previous, concerning associations of neonatal phototherapy with increased risk of any cancer, nonlymphocytic leukemia, or brain and/or central nervous systems tumors after 4 years of age.

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Phototherapy is commonly used to treat hyperbilirubinemia in newborns. Although it has been widely considered safe, it can damage DNA,[1–4] potentially leading to cancer. There is conflicting evidence of a carcinogenic effect. Multiple studies in Europe found no association with leukemia.[5–7] One Swedish study found an elevated risk for myeloid leukemia, but it was attenuated after excluding cases with Down syndrome (none of the controls had Down syndrome).[8] In a California study, researchers using a large, administrative data set found a slight increased risk for overall cancer, myeloid leukemia, and kidney cancer before age 1 among those who received phototherapy.[9]

Newman et al[10] previously reported on the association of phototherapy and cancer using data from a large cohort of children born from 1995 to 2011 at Kaiser Permanente Northern California (KPNC) hospitals followed through March 2014. The study reported that phototherapy was associated with higher rates of any type of leukemia and nonlymphocytic leukemia in unadjusted models. In propensity-adjusted analyses, however, excess risks were attenuated and no longer statistically significant.

Recently, Auger et al[11–13] reported on the association between phototherapy and childhood cancer using administrative data from the province of Quebec. Their hypothesis was unique compared with previous studies in that they looked for evidence of excess cancers only after a latent period of several years after phototherapy. They found an increased risk particularly for late-onset solid tumors, such as brain and central nervous system (CNS) cancers, between ages 4 and 11 years.

In this report, we update the investigation by Newman et al with an additional 6 years of the birth cohort (now through 2017) and 5 additional years of follow-up (now through March 2019). In addition, we assess whether there is evidence to support the findings by Auger et al of increased risk of later-onset childhood cancer, which was not previously investigated in this population.

METHODS

Study Design and Sample

We assembled a cohort of 751 170 children born at ≥35 weeks' gestation from 1995 to 2017 at KPNC hospitals. We excluded infants who died during their birth hospitalization (n = 463; 0.1%), were transferred to facilities outside of KPNC (n = 1112; 0.2%), had follow-up in KPNC for <60 days (n = 38 442; 5.1%), or were diagnosed with cancer before 60 days or only had a secondary cancer diagnosis (n = 28; <0.01%). An additional 3582 infants (0.5%) were excluded because the last encounter date was missing and another 4901 (0.7%) because of missing covariate data. We categorized these 702 646 children into neurotoxicity risk groups on the basis of gestational age (dichotomized at 38 weeks) and direct antiglobulin test (positive or not) and compared all of their total serum bilirubin (TSB) levels to the relevant phototherapy thresholds in the 2004 American Academy of Pediatrics (AAP) phototherapy guidelines.[14] We then restricted the sample to those with a qualifying bilirubin level, defined (as in previous studies[10,15]) as a TSB −3 mg/dL to +4.9 mg/dL from the relevant AAP threshold. A final analytic sample of 139 100 children remained. This is 40 780 more children than included in the models restricted to this TSB range in the previous analysis by Newman et al.[10]

The institutional review boards for the protection of human subjects at the University of California, San Francisco, (no. 10-04918) and KPNC (no. 1270417-19) approved the study.

Exposure

The exposure of interest was a binary indicator of receiving any phototherapy during birth hospitalization or readmission. For infants born before the implementation of HealthConnect (the Kaiser Permanente version of EPIC, the electronic health record), phototherapy use was ascertained from inpatient procedure codes. For infants born after the implementation of HealthConnect, phototherapy use was determined on the basis of documentation in a phototherapy nursing flowsheet or both a procedure code and an order for phototherapy.

Covariates

We obtained data on hypothesized confounders from medical records: sex, race and/or ethnicity (White, Asian American, Black, Hispanic, and other or unknown), gestational age (weeks), delivery mode (normal spontaneous vaginal, assisted vaginal, and cesarean), facility of birth, year of birth, maternal age (<25, 25–34, and ≥35 years), multiple birth, birth weight (grams), Down syndrome, presence of congenital anomalies, chromosomal abnormalities other than Down syndrome, early hyperbilirubinemia (an indicator for a TSB level within 3 mg/dL of the phototherapy threshold before 24 hours of age), and TSB level in relation to the phototherapy threshold categorized in 1.0-mg/dL increments.[10,15] Race and/or ethnicity was included because Asian American infants are more likely to be diagnosed with jaundice and more likely to require phototherapy than white infants.[16] Furthermore, there are known racial

and/or ethnic disparities in cancer incidence.[17–19]

We converted *International Classification of Diseases, 10th Revision* codes to *International Classification of Diseases, Ninth Revision*, (ICD-9), if needed, and classified subjects as having congenital anomalies or chromosomal abnormalities based the presence of at least 2 ICD-9 codes from inpatient or outpatient encounters from unique departments or dates: Down syndrome (ICD-9: 758.0), other chromosomal abnormalities (758.1–758.9), and congenital anomalies (740–759.9, except 743.65 [nasolacrimal passage anomaly]).

Outcomes

Childhood cancer was captured via diagnosis codes from all inpatient and outpatient encounters. We required at least 2 diagnoses of cancer from different departments or different dates to reduce false-positive diagnoses because of coding errors. The modal cancer ICD-9 code (recorded at the highest number of encounters) was the diagnosis used for this study. Age at event time was defined as age at the first diagnosis of cancer. We excluded cancers occurring before 60 days of age to allow for a minimum latent period between phototherapy and the development of cancer.[9–11]

We classified cancer into hematopoietic cancers: (1) acute lymphocytic leukemia (ICD-9: 204.X), (2) nonlymphocytic leukemia (205.0–208.X), and (3) lymphoma and other hematopoietic cancers (200.0–202.X); solid tumors: (1) brain and CNS tumors (190.5, 191.0–192.X) and (2) other solid tumors (140.0–165.X, 170.0–171.X, 174.0–189.X, 190.9, and 193.0–196.X); and other cancers (172.0–173.X and 199.0).

Follow-up Time

Time at risk in primary analyses was defined as starting at age 60 days and ending at the age of first cancer diagnosis or censored at the age of the last encounter date at a KPNC facility through March 16, 2019. This resulted in a total of 1 112 520 person-years (453 786 more than the original cohort).

Statistical Methods

Our logistic models for propensity for inpatient phototherapy included sex, race, gestational age, delivery mode, facility of birth, year of birth, maternal age, multiple birth, birth weight (as restricted cubic splines), chromosomal abnormalities (other than Down syndrome), early hyperbilirubinemia, and bilirubin levels in relation to guidelines. Because those with Down syndrome are at greatly increased risk for hematopoietic cancers, we did not include Down syndrome in the propensity model we used for all cancer and hematopoietic cancer and instead included it separately in the outcome model to ensure adequate control of confounding. We included Down syndrome in the propensity model for solid tumors.

We calculated crude incidence rate ratios for cancer among those who did and did not receive phototherapy. We then used Cox proportional hazard regression to estimate the effect of phototherapy on the hazards of each type of cancer controlling for quintiles of propensity to receive phototherapy. We tested the proportional hazards assumption on the basis of Schoenfeld residuals. In all models, we controlled for congenital abnormalities and, in models for any cancer and hematopoietic cancers, for Down syndrome as well. As a sensitivity analysis, we estimated the same models with time 0 beginning at 1 year of age, rather than 60 days, to further preclude the possibility of reverse causation.

To assess whether there was a higher risk for late-onset cancers, we used the same Cox models but allowed time-varying exposure effects. To facilitate comparisons with the results of Auger et al,[11] we added an interaction term, with age dichotomized at 4 years. We conducted a sensitivity analysis in which we added an interaction term, with age dichotomized at 6 years instead. We also used the propensity scores to create stabilized inverse probability weights and re-estimated all models as weighted analyses.

Finally, we restricted our exposure to birth hospitalization phototherapy (excluding those who were readmitted for phototherapy) to assess if this had any impact on the results of the primary analyses.

RESULTS

A description of the cohort is included in Table 1. Of the 139 100 newborns with qualifying bilirubin levels included in the study, 42 266 (30.4%) received phototherapy. Infants who did and did not receive phototherapy differed in the expected ways.

Cancer incidence rates and crude incidence rate ratios (IRRs) are presented in Table 2. Graphs of the crude cumulative incidence for each type of cancer are included as Supplemental Figs 1–10. In unadjusted analyses, any cancer (IRR: 1.31, 95% confidence interval [CI]: 0.99–1.72), any hematopoietic cancer (IRR: 1.65, 95% CI: 1.10–2.47), and acute lymphocytic leukemia (IRR: 1.72, 95% CI: 1.03–2.84) were associated with phototherapy. Only 9 children diagnosed with nonlymphocytic leukemia received phototherapy: reclassification of leukemia cases based on the modal rather

TABLE 1 Description of Analytic Cohort

	Inpatient Phototherapy	No Inpatient Phototherapy	*P*
n	42 266	96 834	—
Male sex, *n* (%)	23 519 (55.6)	51 913 (53.6)	<.001
Race and/or ethnicity, *n* (%)			<.001
White	13 871 (32.8)	35 383 (36.5)	—
Asian American	13 182 (31.2)	26 127 (27.0)	—
Black	2116 (5.0)	4510 (4.7)	—
Hispanic	9823 (23.2)	22 381 (23.1)	—
Other or unknown	3274 (7.7)	8433 (8.7)	—
Early hyperbilirubinemia: TSB level within 3 mg/dL of AAP phototherapy threshold at <24 h, *n* (%)	12 585 (29.8)	18 519 (19.1)	<.001
Gestational age, wk, *n* (%)			<.001
35	3939 (9.3)	3167 (3.3)	—
36	4870 (11.5)	7318 (7.6)	—
37	6547 (15.5)	16 415 (17.0)	—
38	7069 (16.7)	15 566 (16.1)	—
39	9835 (23.3)	25 404 (26.2)	—
40	6945 (16.4)	20 330 (21.0)	—
≥41	3061 (7.2)	8634 (8.9)	—
Birth wt, kg, mean (SD)	3.3 (0.6)	3.3 (0.5)	<.001
Delivery mode, *n* (%)			<.001
Normal spontaneous vaginal	10 941 (25.9)	20 091 (20.7)	—
Cesarean	26 987 (63.9)	68 104 (70.3)	—
Assisted vaginal	4338 (10.3)	8639 (8.9)	—
Maternal age, y, *n* (%)			<.001
<25	6682 (15.8)	16 603 (17.1)	—
25–34	25 226 (59.7)	58 244 (60.1)	—
35+	10 358 (24.5)	21 987 (22.7)	—
Multiple birth, *n* (%)	1241 (2.9)	2617 (2.7)	.015
Trisomy 21, *n* (%)	262 (0.6)	205 (0.2)	<.001
Other chromosomal anomaly, *n* (%)	169 (0.4)	219 (0.2)	<.001
Other congenital anomaly, *n* (%)	5347 (12.7)	9949 (10.3)	<.001
Included in previous cohort,[a] *n* (%)	30 716 (72.7)	66 494 (68.7)	<.001
Follow-up time, y, mean (SD)	7.8 (5.3)	8.1 (5.9)	<.001

[a] There are 41 890 children included in the present cohort who were not included in the previous publication by Newman et al.[10] This resulted in a total of 40 780 more children in this cohort because the eligibility criteria for our study differed slightly from those in the previous one (required to have nonmissing values for the variables in our propensity score), excluding 1110 children included in the previous cohort. —, not applicable.

than the first cancer diagnosis led to a net decrease of 2 cases exposed to phototherapy compared with what was previously reported for the 1995–2011 cohort. Restricting to those eligible for this study, the percentage of those with nonlymphocytic leukemia exposed to phototherapy decreased from 64.7% in the 1995–2011 cohort to 42.9% in the present cohort.

After adjustment for confounding variables using propensity-score quintiles, none of these associations remained statistically significant (Table 3). The association between phototherapy and any cancer (hazard ratio [HR]: 1.13, 95% CI: 0.83–1.54), as well as any hematopoietic cancer (HR: 1.17; 95% CI: 0.74–1.83), was attenuated. The point estimate for the adjusted HR for nonlymphocytic leukemia decreased to 0.72 (95% CI: 0.26–1.95). Of note, major contributors to the difference between this adjusted HR and the crude IRR (1.78) were Down syndrome and early hyperbilirubinemia. Omitting the propensity-score quintiles and including only these 2 variables brought the adjusted HR down to 0.98 (95% CI: 0.40–2.39). HRs for all categories of solid tumors were close to 1. There was no evidence to reject the proportional hazards assumption. Estimates from models with a latent period of 1 year (instead of 60 days) were similar (Supplemental Table 5).

In models that allowed for time-varying hazards (Table 4), we similarly found no evidence for increased risk of cancer, either before or after 4 years of age. Dividing the follow-up period at age 6 years similarly revealed no evidence for increased cancer related to phototherapy (Supplemental Table 6).

Models adjusting for phototherapy propensity using inverse probability weighting rather than indicator variables for quintiles of phototherapy propensity yielded similar results, although generally with wider CIs (Supplemental Tables 7–10). Changing the exposure to birth hospitalization phototherapy alone also did not appreciably affect the results (results not shown).

TABLE 2 Crude Cancer Incidence Rates and Rate Ratios for Inpatient Phototherapy

	Phototherapy		No Phototherapy			
Cancer	No. Cancers	Incidence of Cancer per 100 000 Person-Years (95% CI)	No. Cancers	Incidence of Cancer per 100 000 Person-Years (95% CI)	Unadjusted Incidence Rate Ratio (95% CI)	*P*
Any cancer	83	25.12 (20.26–31.15)	150	19.18 (16.34–22.51)	1.31 (0.99–1.72)	.05
Any hematopoietic cancer	44	13.32 (9.91–17.89)	63	8.06 (6.29–10.31)	1.65 (1.10–2.47)	.01
Acute lymphocytic leukemia	29	8.78 (6.10–12.63)	40	5.11 (3.75–6.97)	1.72 (1.03–2.84)	.03
Other hematopoietic cancers	15	4.54 (2.74–7.53)	23	2.94 (1.95–4.43)	1.54 (0.75–3.09)	.20
Nonlymphocytic leukemia	9	2.72 (1.42–5.23)	12	1.53 (0.87–2.70)	1.78 (0.66–4.59)	.20
Lymphoma and other hematopoietic cancers	6	1.82 (0.82–4.04)	11	1.41 (0.78–2.54)	1.29 (0.39–3.81)	.61
Any solid tumor	36	10.90 (7.86–15.10)	83	10.61 (8.56–13.16)	1.03 (0.67–1.54)	.89
Brain and CNS tumors	14	4.24 (2.51–7.15)	35	4.48 (3.21–6.23)	0.95 (0.47–1.80)	.88
Other solid tumors	22	6.66 (4.38–10.11)	48	6.14 (4.63–8.14)	1.08 (0.62–1.83)	.74
Other cancer[a]	3	0.91 (0.29–2.82)	4	0.51 (0.19–1.36)	1.78 (0.26–10.49)	.47

[a] Skin cancer ($n = 6$) and unspecified cancer ($n = 1$).

DISCUSSION

In this study, we assessed the effect of phototherapy on childhood cancer, with a particular focus on possible delayed or latent effects. We found no evidence for an increased risk of cancer due to phototherapy. All crude associations between phototherapy and cancer were attenuated after controlling for confounding, similar to the original results by Newman et al.[10] Their results were particularly concerning for nonlymphocytic leukemia; in this analysis, with more patients, extended follow-up time, and use of the modal rather than the first cancer diagnosis, we did not replicate this result. Using the modal diagnosis likely reduced misclassification because patients' initial cancer diagnoses may change or become more specific after biopsies or other tests are completed. We also found no increased risk for any hematopoietic cancer (any leukemia in the earlier paper).

We did not confirm the main results by Auger et al[11] of increased risk of late-onset childhood cancer at older

TABLE 3 Association of Phototherapy and Childhood Cancer in KPNC and Quebec

	KPNC (1995–2017)		Quebec (2006–2016)	
Cancer	No. Cancers	Adjusted HR (95% CI)	No. Cancers	Adjusted HR (95% CI)
Any cancer	233	1.13 (0.83–1.54)	183	1.11 (0.80–1.54)
Any hematopoietic cancer	107	1.17 (0.74–1.83)	61	1.19 (0.70–2.03)
Acute lymphocytic leukemia	69	1.37 (0.78–2.39)	36	1.66 (0.86–3.21)
Other hematopoietic cancers	38	0.89 (0.42–1.89)	<30	0.60 (0.24–1.53)
Nonlymphocytic leukemia	21	0.72 (0.26–1.95)	—	—
Lymphoma and other hematopoietic cancers	17	1.17 (0.37–3.69)	—	—
Any solid tumor	119	1.01 (0.65–1.58)	123	1.05 (0.70–1.60)
Brain and CNS tumors	49	0.94 (0.46–1.93)	50	1.26 (0.70–2.28)
Other solid tumors	70	1.06 (0.60–1.86)	74	0.89 (0.49–1.59)
Other cancer	7	4.13 (0.88–19.43)	—	—

Results from this cohort (KPNC born in 1995–2017, $N = 139\,100$) are compared with Quebec (born 2006–2016, $N = 124\,169$)[11] phototherapy versus untreated jaundice results. All propensity models included sex, race, gestational age, delivery mode, facility of birth, year of birth, maternal age, multiple birth, birth weight, chromosomal abnormalities, early jaundice, and bilirubin. Down syndrome was included in the propensity model for solid tumors. We estimated all Cox proportional hazard models, controlling for propensity-score quintiles and congenital abnormalities, with time at risk beginning at 60 d of age. In models for any cancer and hematopoietic cancers, we also controlled for Down syndrome. —, not applicable.

TABLE 4 Association of Phototherapy and Childhood Cancer in KPNC and Quebec, Allowing Hazards to Vary at Age 4 Years to Assess for Latent Cancer

	KPNC (1995–2017)				
	0–4 y		4+ years		Quebec (2006–2016): 4–11 y, Adjusted HR (95% CI)
Cancer	No. Cancers	Adjusted HR (95% CI)	No. Cancers	Adjusted HR (95% CI)	
Any cancer	122	1.08 (0.72–1.61)	111	1.19 (0.78–1.80)	2.21 (1.31–3.69)
Any hematopoietic cancer	54	1.13 (0.63–2.05)	53	1.20 (0.66–2.18)	2.07 (0.90–4.74)
Acute lymphocytic leukemia	33	1.22 (0.58–2.61)	36	1.51 (0.73–3.10)	2.19 (0.82–5.90)
Other hematopoietic cancers	21	0.98 (0.38–2.52)	17	0.79 (0.27–2.29)	1.14 (0.27–4.69)
Nonlymphocytic leukemia	18	0.74 (0.26–2.14)	3	0.58 (0.05–6.68)	—
Lymphoma and other hematopoietic cancers	3	1.01 (0.09–11.97)	14	1.20 (0.35–4.15)	—
Any solid tumor	66	0.97 (0.55–1.71)	53	1.07 (0.57–2.00)	2.21 (1.15–4.26)
Brain and CNS tumors	22	1.06 (0.40–2.80)	27	0.85 (0.33–2.16)	2.48 (1.04–5.92)
Other solid tumors	44	0.92 (0.46–1.85)	26	1.34 (0.57–3.13)	1.81 (0.67–4.87)
Other cancer	2	5.57 (0.34–91.63)	5	3.65 (0.58–22.83)	—

Results from this cohort (KPNC born in 1995–2017) are compared with Quebec[11] (born 2006–2016) phototherapy versus untreated jaundice results. All propensity models included sex, race, gestational age, delivery mode, facility of birth, year of birth, maternal age, multiple birth, birth weight, chromosomal abnormalities, early jaundice, and bilirubin. Down syndrome was included in the propensity model for solid tumors. We estimated all Cox proportional hazard models, controlling for propensity-score quintiles and congenital abnormalities, allowing hazards to vary at 4 y of age. In models for any cancer and hematopoietic cancers, we also controlled for Down syndrome. —, not applicable.

ages in Quebec. Our goal was to attempt to replicate their results by using a target trial emulation[20,21] approach with inclusion criteria that restricted to infants who ever had an eligible TSB, as defined above. The subset of the infants in this analytic sample who received phototherapy corresponds to the sample of infants in the study by Auger et al who received phototherapy, and the subset who did not receive phototherapy is comparable to the Auger et al sample of untreated infants with jaundice. KPNC incidence of any type of cancer among those who received phototherapy (25.1 per 100 000 person-years) matched Quebec's (25.1 per 100 000 person-years). The incidence rate of any cancer among those with jaundice who did not receive phototherapy was 19.2 per 100 000 person-years at KPNC versus 23.0 per 100 000 person-years in Quebec.

Point estimates and CIs from our primary models controlling for confounding were, in general, similar to those of Auger et al.[11] However, our point estimates for cancer after 4 years of age were consistently lower than the estimates by Auger et al. For their most concerning results, which indicated increased risk of both solid tumors and brain and/or CNS tumors, our estimated 95% CIs for ages 4 and older excluded their point estimates. In some cases, our point estimates for the hazard of cancer associated with phototherapy from 0 to 4 years differed from 4+ years. For example, for acute lymphocytic leukemia, the HR was 1.22 (0.58–2.61) from 0 to 4 years and 1.51 (0.73–3.10) for 4+ years of age. This could be chance variation or a true increase in risk that we did not have enough power to detect.

We replicated the methods by Auger et al as closely as possible. Our propensity models included all of the same variables, with the exception of place of residence (rural <10 000 inhabitants, urban, and unspecified) and socioeconomic deprivation in their analyses and early hyperbilirubinemia and bilirubin levels in our analyses, which they did not have access to in their data set. Although we controlled for propensity-score quintiles in our primary analyses, based on the previous analysis by Newman et al,[10] we also estimated models with stabilized inverse probability weights to ensure that did not explain any observed differences with Auger et al. Our results from the weighted models were qualitatively similar to our results from primary analyses. Both the Quebec study and our own controlled for congenital anomalies directly in the outcome models; however, we also decided to control for confounding by Down syndrome directly in the outcome models for hematopoietic cancers because it is a strong risk factor. Our results likely differ not because of our methodologic choices but rather because the associations they detected in their cohort were not present in ours.

Childhood cancer is a rare disease, and there are a small number of cases of cancer, although the cohort was large. We hypothesized that

given the increased sample size and additional years of follow-up of the extended data set that we would be able to achieve more precise estimates, but wide CIs continued to preclude the ability to fully rule out a small effect of phototherapy on cancer risk. Additionally, the data set lacks information on dosage and intensity of phototherapy. In addition, fluorescent and incandescent light was used in much of the phototherapy provided during the study, whereas LED light is primarily used in modern phototherapy. The measurement of cancer incidence is also undoubtedly imperfect, although its specificity (by requiring 2 diagnoses of cancer) is likely to be high. In addition, this measurement error is unlikely to be worse than that of Auger et al, so this does not explain the discrepancy in results. We did not have information on morphology, which is a particular limitation for the interpretation of estimates of the association between phototherapy and specific solid tumors. It is possible, for example, that the HRs for brain and CNS tumors were slightly attenuated if some brain metastases were erroneously coded as primary brain tumors. However, because we used only the modal diagnosis of cancer, we expect this misclassification and its effects on our HRs to be minimal. We also did not have data on other causes of cancer (eg, cancer predisposition syndromes, prenatal exposures to radiation, cytomegalovirus, or pesticides). However, to account for our null findings, factors that increase cancer risk would have to be reasonably common and to decrease the use of phototherapy. Given that treatment decisions about phototherapy are mostly based on the variables included in our models and that these syndromes and exposures are rare, generally diagnosed well after birth, and unlikely to decrease phototherapy use, significant confounding from such factors is unlikely. Finally, we do not know whether those who left KPNC developed childhood cancer, but there is no reason to believe the association between phototherapy and cancer rates would be different among this group.

CONCLUSIONS

In a large cohort of children in Northern California, we found no evidence for increased risk of cancer due to phototherapy. In addition, we did not replicate previous, concerning findings of increased risk of nonlymphocytic leukemia[10] or of brain and/or CNS tumors in later childhood.[11] Although a small causal effect is possible, we believe current evidence suggests that the decision to treat with phototherapy should be based on other, more compelling considerations.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
CI: confidence interval
CNS: central nervous system
HR: hazard ratio
ICD-9: *International Classification of Diseases, Ninth Revision*
KPNC: Kaiser Permanente Northern California
TSB: total serum bilirubin

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