Association between neonatal phototherapy and future cancer: an updated systematic review and meta-analysis

Running title: Phototherapy and cancer

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Abstract

Purpose: Phototherapy is the main treatment of neonatal hyperbilirubinemia to prevent encephalopathy. It is generally believed to be safe; however, some studies have shown it might be associated with cancer development. In this systematic review and meta-analysis, we aimed to assess the effect of neonatal phototherapy on future cancer risk.

Methods: A systematic search in 13 databases was conducted in December 2018 and updated in August 2022 to identify studies that report cancer development after exposure to phototherapy. Throughout the study period, regular manual searches were also conducted to include new studies. A meta-analysis using R programming language was done in which the odds ratios (ORs) with 95% confidence intervals (CIs) were estimated and pooled using the reported adjusted and unadjusted data.

Results: Fifteen studies were included. A statistically significant association was detected between neonatal phototherapy and any type of cancer (OR 1.24; 95% CI 1.1, 1.4), any hematopoietic cancer (OR 1.49; 95% CI 1.17, 1.91), any leukemia (OR 1.35; 95% CI 1.08, 1.67), and myeloid leukemia (OR 2.86; 95% CI 1.4, 5.84). The other investigated cancers (lymphoid leukemia, Hodgkin's lymphoma, kidney cancer, nervous system cancer, and skin cancer) were not associated with phototherapy.

Conclusions: Phototherapy may carry a possible risk of future cancers. Future research is needed to quantify the magnitude of the cancer risk. These future studies should consider predictors of preterm birth or exclude premature babies from their analysis.

What is Known

- There were various reports about the possible association between phototherapy in neonates and the increased risk of cancer in the future.

What is New

- A statistically significant association between phototherapy and various hematopoietic cancers (especially myeloid leukemia) was recorded.
- The effect of the duration of phototherapy on the increased risk of hematopoietic cancers is yet unclear.
- There is not yet sufficient evidence revealing the effect of phototherapy on cancer risk in preterm babies. Therefore, studies excluding preterm babies or conducting subgroup analyses of them are necessary.

Keywords

Phototherapy; neoplasms; infant; newborn; leukemia; kidney neoplasms

Abbreviations

CI: confidence interval

GHL: Global Health Library

ICD: International Classification of Diseases

NHL: Non-Hodgkin's lymphoma

NIH: National Institutes of Health

NYAM: New York Academy of Medicine

OR: odds ratio

PRISMA: Preferred Reporting Items for Systematic review and Meta-Analysis statement

PT: phototherapy

SD: standard deviation

SIGLE: System for Information on Grey Literature in Europe

VHL: Virtual Health Library

WHO: World Health Organization

Background

Phototherapy is the use of light, in its visible form, for the treatment of jaundice in newborns [1]. For more than 60 years, it has been used as the standard treatment for neonatal hyperbilirubinemia [2]. Except for prophylactic measures, phototherapy is likely the most commonly used treatment in newborn infants [2]. Phototherapy aims to prevent the rise of serum bilirubin levels and has markedly decreased the number of cases needing exchange transfusion to prevent bilirubin encephalopathy, which causes permanent neurological damage [3]. The understanding of the mechanisms of phototherapy has increased significantly during the past 30-40 years [2; 4; 5]. Phototherapy acts on bilirubin, which is present in the superficial capillaries and interstitial spaces in the skin, by converting it into water-soluble isomers that can easily be excreted without further hepatic metabolism [2].

Despite being generally considered safe, phototherapy has been associated with some short-term adverse events, such as alteration of circadian rhythm, dehydration, hypocalcemia, skin rash, hemolysis, altered hemodynamics, and retinal injury [6]. In addition, some studies have shown a possible association between phototherapy and subsequent cancers [7-9]. This has been challenged by studies that have found no evidence of increased risk [10-12].

Objectives

We aimed to perform a systematic review and meta-analysis of relevant articles to assess the association between neonatal phototherapy for the treatment of neonatal jaundice and any type of cancer.

Methods

Search strategy

We performed our study according to the recommendations of the widely accepted Preferred Reporting Items for Systematic Review and Meta-Analysis statement 2020 (PRISMA) (Supplementary Table 1) [13; 14]. The protocol has been registered in the PROSPERO database with ID (CRD42019131025).

Data Sources

A comprehensive search in 13 databases including PubMed, Scopus, Web of Science (ISI), EMBASE, Google Scholar, Cochrane Library, Virtual Health Library (VHL), WHO Global Health Library (GHL), POPLINE, System for Information on Grey Literature in Europe (SIGLE), mRCT, Clinical trial, and NYAM was performed in December 2018 and updated in August 2022. The search terms used were Phototherapy AND (neonatal OR

neonate OR newborn) AND (cancer OR malignancy OR malignant OR melanoma OR neoplasm OR neoplastic OR neoplasia OR tumor) AND (risk OR risks OR association OR associated OR correlation). A detailed search strategy for each database is available in Supplementary Table 2.

Study Selection

Three reviewers independently conducted the database search and title-and-abstract screening. The potential full-text articles were further checked according to the predefined inclusion and exclusion criteria. No restrictions were made on study designs including, date of publication, country, gender, and language. Any article containing data on the association between phototherapy and cancer was included. The exclusion criteria included *in-vitro* and animal studies, duplicated, and abstract-only articles. If the abstract was included by any of the three reviewers, the full-text article was carefully reviewed by all three reviewers for any potentially relevant data. In case of disagreement, the final decision was made through discussion. An additional manual literature search was conducted in January 2019, leading to the inclusion of four more articles [7; 10; 11; 15]. The manual search included a simple search in PubMed and Google Scholar and searching references of the included articles and other related reviews.

Data extraction

Using independent data extraction methods, three reviewers have independently extracted information. Any disagreements have been resolved through discussion and consensus. A data extraction template was created using Microsoft Excel by extracting and calibrating data from the finally included studies. The extracted data included demographic characteristics of patients and outcomes of interest, in addition to authors' names, year of recruitment, study design, year of publication, and data collection method.

Quality assessment

Three authors assessed the quality of the studies independently. Discrepancies were resolved through discussion in conjunction with the senior authors. We used either "NIH-Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies", or "NIH-Quality Assessment of Case-control Studies" according to the study type [16]. A total score was given to each study according to the answer to each question (Yes = 1, No = 0, Unknown = 0). In the assessment of cohort studies, 10-14 out of 14 points, was an indicator of a good quality article, 5-9 indicated fair quality and 1-4 indicated poor quality [17]. As for case-control studies, 9-13 out of 13 points, indicated a good quality article, 5-8 indicated fair quality and 1-4 indicated poor quality.

Intervention and endpoints

The intervention of interest in the included studies was phototherapy exposure during the neonatal period. The outcomes were any type of cancer, leukemia, and its subtypes, non-Hodgkin's lymphoma, as well as cancers of the liver, skin, bone, nervous system, kidney, eye, and orbit.

Data synthesis

A meta-analysis was performed for the selected outcomes using Comprehensive Meta-analysis software version 3 (Biostat, NJ, USA) when the data were sufficiently comparable. If the outcome is presented in a minimum of two studies, it was considered "Sufficient" to perform the meta-analysis [18]. Dichotomous variables were analyzed to calculate the pooled Odds Ratio (OR) and its 95% confidence interval (95% CI). We calculated the overall estimate by merging unadjusted and adjusted data in one analysis, giving priority to adjusted data if both data were found in the same study. In addition, repeat analyses using unadjusted data only and adjusted data only were performed. Based on the rarity of the presented outcomes in this study, the rate ratios for adjusted data described in the included studies were used in the analysis as adjusted OR [19; 20]. If the 95%CI did not include the null value of 1.0, this was considered statistically significant. Heterogeneity was assessed using Q-statistics of heterogeneity and the associated I-square values. If the P-value was less than 0.1 or the I^2 more than 50%, the data were considered heterogeneous. A fixed-effects model was used when there was a lack of significant heterogeneity, while a random-effects model was used when there was significant heterogeneity between studies [21]. The Egger's regression test and Begg's modified funnel plot were used to examining the presence of publication bias. When the p-value is less than 0.1, publication bias is considered significant [22].

Results

Search results

The PRISMA flow diagram of studies identification and selection is shown in Fig. 1. After using EndNote software to remove duplicates, 467 articles were selected for the title-and-abstract screening, and 46 articles were considered for full-text review. Only fifteen articles met the eligibility criteria. In the final meta-analysis, Wickremasinghe et al.'s study [23] was not included due to possible overlap with Newman's study [24].

Study and participants' characteristics

A total of 7343592 participants were included from eight different countries, namely Sweden [8; 10; 24], the USA [7; 23; 25], the UK [11; 26], Canada [15], Denmark [12], Taiwan [27], Iran [28; 29], and Israel [30]. Among the

fifteen included articles, seven were case-control studies and eight were cohort studies. The basic characteristics of the included studies are shown in Table 1.

Quality assessment

In terms of quality, six case-control studies [8; 10; 11; 24; 28; 29] and three cohort studies [12; 26; 27] were of fair quality, while one case-control study [7] and the remaining cohort studies [15; 23; 25; 30; 31] were of good quality (Table 1 and Supplementary Tables 3 and 4).

Association between neonatal phototherapy and different types of cancer

As mentioned before in the methods, we analyzed the data in three parts, combined data, unadjusted data, and adjusted data, where applicable. Combined data refers to the analysis of adjusted (if found) and unadjusted data.

1. **Any cancer**

Six studies contributed to the analysis of combined data [12; 15; 27; 29-31]. There was a statistically significant association between exposure to phototherapy in the neonatal period and the future development of any type of cancer (OR 1.24; 95% CI 1.1, 1.4) (Fig. 2). There was funnel plot asymmetry (Egger's test P-value = 0.03) (Fig. 3). As for the unadjusted data [15; 27; 29-31], we found no statistically significant association between exposure to phototherapy in the neonatal period and the future development of any type of cancer (OR 1.11; 95% CI 0.87, 1.4). (Supplementary Fig.1). Funnel's plot Egger's test P-value was 0.27 (Supplementary Fig. 2). The same was also found in the adjusted data (OR 1.17; 95% CI 0.99, 1.38) (Supplementary Fig. 3). Funnel's plot Egger's test P-value for adjusted data analyses was 0.07 (Supplementary Fig. 4).

2. **Any Hematopoietic cancer**

Three studies contributed to the analysis of combined data [15; 30; 31]. We found a statistically significant association between exposure to phototherapy in the neonatal period and the future development of any hematopoietic cancer (OR 1.49; 95% CI 1.17, 1.91) (Supplementary Fig. 5). Moreover, comparable results were found in the unadjusted data analysis (OR 1.6; 95% CI 1.21, 2.13) [30; 31] (Supplementary Fig. 6) and the adjusted data analysis (OR 1.43; 95% CI 1.04, 1.96) [15; 30] (Supplementary Fig. 7).

3. **Any leukemia**

Five studies were included in the combined analysis [7; 11; 12; 25; 30]. There was a statistically significant association between exposure to phototherapy in the neonatal period and the future development of any type of

leukemia (OR 1.35; 95% CI 1.08, 1.67) (Fig. 4). The same was observed in the unadjusted data analysis (OR 1.66; 95% CI 1.26, 2.2) [7; 11; 25; 30] (Supplementary Fig. 8) and the adjusted one (OR 1.37; 95% CI 1.1, 1.71) [7; 12; 25; 30] (Supplementary Fig. 9).

4. **Lymphoid leukemia**

Five [10-12; 15; 31], four [10; 11; 15; 31], and two [12; 15] studies reported this outcome in the combined, unadjusted, and adjusted analyses, respectively. There was no statistically significant association between exposure to phototherapy in the neonatal period and the future development of lymphoid leukemia in the three analyses (OR 1.25; 95% CI 0.99, 1.59) (Fig. 5), (OR 1.22; 95% CI 0.88, 1.69) (Supplementary Fig. 10), and (OR 1.21; 95% CI 0.89, 1.65) (Supplementary Fig. 11), respectively.

5. **Myeloid leukemia**

Data from three studies were pooled in the combined and unadjusted analyses [8; 11; 25]. There was a statistically significant association between exposure to phototherapy in the neonatal period and the future development of myeloid leukemia in both analyses (OR 2.86; 95% CI 1.4, 5.84) (Supplementary Fig. 12) and (OR 3.3; 95% CI 1.66, 6.55) (Supplementary Fig. 13), respectively.

6. **Non-Hodgkin's lymphoma**

Two studies were included in this analysis [11; 12]. One presented adjusted data [12] while the other presented unadjusted data [11]. There was no statistically significant association between exposure to phototherapy in the neonatal period and the future development of non-Hodgkin's disease (OR 1.56; 95% CI 0.66, 3.69) (Supplementary Fig. 14).

7. **Kidney cancer**

Data from two studies were presented in this analysis of adjusted data [12; 25]. There was no statistically significant association between exposure to phototherapy in the neonatal period and the future development of kidney cancer (OR 1.20; 95% CI 0.72, 2.02) (Supplementary Fig. 15).

8. **Nervous system cancer**

Data from three studies were presented in this combined analysis [12; 15; 31]. There was no statistically significant association between exposure to phototherapy in the neonatal period and the future development of nervous

system cancer (OR 1.08; 95% CI 0.81, 1.45) (Supplementary Fig. 16). The same was observed in the unadjusted data analysis of two studies [15; 31] (OR 1.12; 95% CI 0.75, 1.69) (Supplementary Fig. 17).

9. **Skin cancer**

Four studies reported this outcome [24-27]. No adjusted data were found in any of these studies. There was no statistically significant association between exposure to phototherapy in the neonatal period and the future development of skin cancer (OR 1.01; 95% CI 0.42, 2.41) (Supplementary Fig. 18).

Discussion

Summary of main results

In this review, associations between neonatal phototherapy and increased cancer risk were found although the analysis of the risk of any cancer had significant heterogeneity with an asymmetric funnel plot. Specifically, any hematopoietic cancer, any leukemia, and myeloid leukemia showed statistically significant associations. Phototherapy in newborns, according to these results, may be associated with increased odds of developing any cancer by 1.2 times, the odds of any hematopoietic cancer by 1.5 times, the odds of leukemias by 1.4 times, and the odds of myelocytic leukemia by 2.9 times.

Agreements and disagreements with other reviews

In a recently published systematic review and meta-analysis, phototherapy was found to be a possible risk factor for any childhood cancer (RR 1.28; 95% CI 1.08, 1.51) and any leukemia (RR 1.33; 95% CI 1.03, 1.71) [32]. While the review included 13 articles, only seven were related to cancer [8; 12; 15; 23-26], while the remaining six studies were about the association between phototherapy and nevi, with no mention of malignant neoplasms [33-38]. And since their database search was done in March 2020, they missed the latest four articles published on the same topic [28-31]. In addition, four more articles were missing from their database search [7; 8; 11; 27]. Lastly, we found that neonatal phototherapy might be associated with any hematopoietic cancer and myeloid leukemia, which were not reported in their studies.

Possible underlying mechanism

In the 1970s, a positive mutagenic effect of phototherapy was reported in prokaryotic and eukaryotic cells [39]. Subsequent *in-vivo* studies in jaundiced, full-term infants confirmed that DNA damage in peripheral blood lymphocytes can result from exposure to phototherapy [40]. The proposed mechanism is the formation of singlet oxygen [41] or free radicals [42] when protoporphyrin in circulating lymphoblasts is exposed to fluorescent light,

239 which can then interact with cellular DNA and cause double or single-strand breaks [43]. Because modification
240 of the cellular DNA could be the basis of carcinogenic potential, an association between phototherapy and cancer
241 has been hypothesized [39].

242 However, a different theory suggested that the carcinogenic effect noticed in neonates receiving phototherapy
243 may be due to hyperbilirubinemia. This was supported by studies that found that high levels of serum bilirubin
244 had genotoxic effects [44; 45]. However, two other studies failed to demonstrate any correlation between bilirubin
245 and oxidative stress or DNA damage scores [46; 47].

246 Some of the included studies have provided data regarding jaundiced babies who received phototherapy and those
247 who did not receive it [7; 8; 10; 11; 15; 27]. The association between hyperbilirubinemia and future cancers cannot
248 be excluded by comparing these two groups as the level of bilirubin in the newborns who received phototherapy
249 is most likely higher than those in jaundice without the phototherapy group.

250 However, it is also still questionable whether phototherapy is truly the cause of cancer, or simply a result of the
251 same underlying factors that gave rise to cancer. The association between different types of cancer and birth
252 weight has been observed in a variety of studies in adults and children. High birth weight is associated with
253 lymphoid leukemias, astrocytomas, and kidney cancer, while acute myeloid leukemia has a U-shaped relationship
254 with birthweight [48; 49]. Many studies also linked cancers to certain congenital anomalies, prematurity, small or
255 large-for-gestational age, restricted fetal growth metrics (head size, abdominal circumference, Ponderal index),
256 and pregnancy complications such as gestational diabetes [50-55]. Many of these risk factors are also predictors
257 of phototherapy.

258 Another potential explanation may be speculated based on findings of several genetic variants in bilirubin
259 metabolism that may contribute to the high serum bilirubin levels seen in babies who require treatment with
260 phototherapy [56-59]. Hypothetically, these genetic variants might also be involved in mechanisms leading to
261 cancer. If so, phototherapy may be nothing more than a marker for the underlying mechanism.

262 **Implications of the results in clinical research and practice**

263 Phototherapy use with the current treatment thresholds has nearly obviated the need for exchange transfusion and
264 is currently the mainstay of therapy for the treatment of neonatal jaundice [2]. However, because of the general
265 belief in the safety of phototherapy and the fear of bilirubin toxicity, phototherapy has frequently been used below
266 the recommended thresholds [60; 61]. This practice will necessarily lead to longer exposure to the phototherapy

lights, which in vulnerable premature infants, may be associated with increased mortality [62; 63]. Whether such prolonged exposure is also involved in cancer risk, is yet unknown. It is important to consider that to prevent one newborn from having an exchange transfusion, the number needed to treat with phototherapy is in the hundreds or thousands [64]. For term and near-term infants, there is little to no risk of cerebral palsy [65] or hearing loss [66] unless the bilirubin level is 10 mg/dL (170 micromol/L) or more above the exchange transfusion thresholds. Thus, any rare side effects, including the increased risk of cancer, require more evaluation and, if it is real, would warrant a more conservative use of phototherapy.

Limitations

One limitation of our analysis is the small number of studies included in some cancer types. In addition, many of the included studies did not control for predictors of preterm birth, and/or exclude preterm births from their population, as a large proportion of these births receive phototherapy. The variation in age between studies may also account for the difference in their outcomes as early cancers may be more associated with perinatal events. Furthermore, the included studies include a variety of cancer types under the same outcome, such as nervous system tumors. Finally, all included studies were conducted retrospectively or based on a case registry. This precludes us from properly assessing a causal relationship between phototherapy and cancer, especially when other possible confounding factors (age at diagnosis, preterm birth) do not present an intermediate step between the exposure (phototherapy) and outcome (cancer). Moreover, some of these factors, especially preterm birth, can affect the duration of phototherapy, further complicating the proper assessment of causality.

Many phototherapy delivery systems are commercially available and differ in many characteristics. Thus, they may use different types of lamps, and the intensity of the light (irradiance) may vary, as may the wavelength peak and spectral distribution.[2] The question of whether these factors might affect the incidence of childhood cancer or not is important. However, the studies included in our analyses did not provide sufficient data regarding the type of light sources, or the different wavelengths used, making it impossible to analyze this important question. Additionally, data on home phototherapy may be missing in some of the included articles. Another limitation of our review is the fact that all of the included studies were observational. We were also unable to adjust for potential confounding variables not described in the included studies. A final concern is the asymmetric funnel plot found in the analysis of the association of any cancer with phototherapy. Although this might limit the conclusion of the presence of true association, the absence of heterogeneity in other analyses may contradict this limitation.

Conclusion

Phototherapy could be a possible risk factor for cancer in general, any leukemia, and myeloid leukemia in particular. This association needs to be further explored in future studies. Upcoming studies should control for other risk factors for cancer, including preterm delivery. Until this relationship has been resolved, phototherapy should be used only according to standard treatment guidelines. Should phototherapy be used below the standard threshold, the reasons for its use should be strongly justified and documented.

Figure legends

Figure 1. PRISMA flow diagram of studies' screening and selection.

Figure 2. Meta-analysis of the association between phototherapy and the future development of any cancer (adjusted and unadjusted data).

Figure 3. Egger's plot for any type of cancer (adjusted and unadjusted data)

Figure 4. Meta-analysis of the association between phototherapy and the future development of any leukemia (adjusted and adjusted data)

Figure 5. Meta-analysis of the association between phototherapy and the future development of lymphoid leukemia (adjusted and unadjusted data)

Tables

Table 1. Characteristics of the included studies

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Author contributions

NTH developed the idea. All authors screened the articles for eligibility and collected the data using the standardized extraction Excel sheet. MA, AMM, and NTH performed the data analysis. MA created the tables and figures. All authors contributed to writing the manuscript. All authors approved of the final version of the manuscript before submission for publication.

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Not applicable.

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Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available. However, the data can be provided by the corresponding author (Nguyen Tien Huy; tienhuy@nagasaki-u.ac.jp) on reasonable request.