RESEARCH ARTICLE

Breastfeeding and the Risk of Childhood Hodgkin Lymphoma: A Systematic Review and Meta-analysis

Ke-Lai Wang[&], Chun-Lan Liu[&], Yan Zhuang*, Hong-Yi Qu

Abstract

Purpose: Numerous observational epidemiological studies have evaluated associations between breastfeeding and the risk of childhood Hodgkin lymphoma; however, the existing results are inconsistent. We therefore conducted a systematic review and meta-analysis. Methods: Medical literature was searched in the Pubmed and Embase databases to identify all English-language relevant studies up to April 10, 2013. Reference lists were thereafter hand-searched for additional articles. Studies that reported relative risk ratios (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were included. This meta-analysis was conducted in accordance with the guidelines for the meta-analysis of observational studies in epidemiology. Results: We finally included 10 case-control studies in our meta-analysis, involving 1,618 childhood Hodgkin lymphoma cases and 8,181 controls. Overall, we did found a borderline significant association between breastfeeding and reduced risk of childhood Hodgkin lymphoma comparing ever breastfed children to never breastfed children (pooled OR =0.79; 95%CI, 0.58-1.08; *P*=0.13), with limited evidence for between-study heterogeneity (*P* =0.12, I^2 = 35.70%). Conclusion: There is limited evidence for an inverse association between breastfeeding and risk of childhood Hodgkin lymphoma.

Keywords: Breastfeeding - childhood Hodgkin lymphoma - meta-analysis - case-control studies

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Introduction

The incidence of Hodgkin lymphoma has increased among adolescents and young adults, but decreased significantly in recent decades among the elderly in Western countries; the cause of childhood Hodgkin lymphoma is only partially understood (Nakatsuka et al., 2006; Landgren et al., 2007; Hjalgrim et al., 2012). There is increasing evidence that relevant risk factors in early life are associated with childhood Hodgkin lymphoma.

The benefits of breastfeeding for children are well-known. Indeed, breastfeeding affects cancer, obesity, diabetes mellitus, and cardiovascular disease, in addition to reducing episodes of diarrhea, decreasing the incidence of infections (enteric, otitis media, and respiratory infections) and eczema (Oddy et al., 2003; Paramasivam et al., 2006; Das, 2007; Ip et al., 2007; Hosea Blewett et al., 2008; Monterrosa et al., 2008; Rosenbauer et al., 2008; Ladomenou et al., 2010). Some epidemiologic studies during the last 3 decades have focused on the association between breastfeeding and the risk of childhood Hodgkin lymphoma. Although several studies have shown that breastfeeding has a protective effect on childhood Hodgkin lymphoma, the data is controversial.

The aim of this meta-analysis was to synthesize current evidence derived from all case-control and cohort studies regarding the association between breastfeeding and the risk of childhood Hodgkin lymphoma.

Materials and Methods

Search Strategy

Related publications were systematically searched up to November 2012 in the PubMed and Embase databases without restrictions using the following items: pediatric or children or child or childhood and lymphoma or cancer or Hodgkin and breastfeeding or infant feeding. In addition, reference lists were systematically searched for relevant articles. The present meta-analysis was conducted in accordance with the guidelines for the meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al., 2000).

Eligibility Criteria

Studies were included in the meta-analysis if the following criteria were met: (1) published in the English language; (2) the exposure of interest was breastfeeding; (3) the outcome of interest was childhood Hodgkin lymphoma; (4) estimates of the relative risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs)

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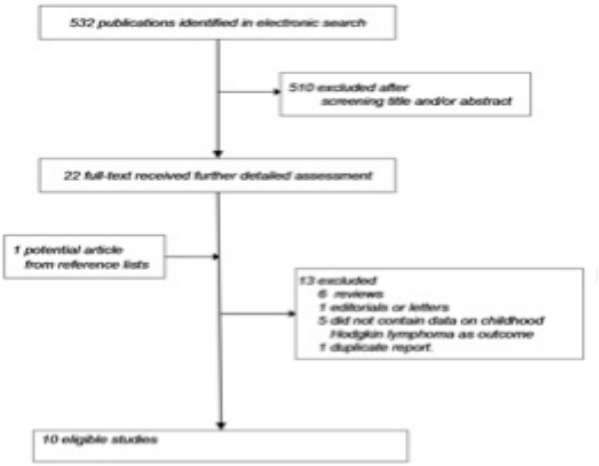

Figure 1. Selection of Studies for Inclusion in Meta-analysis

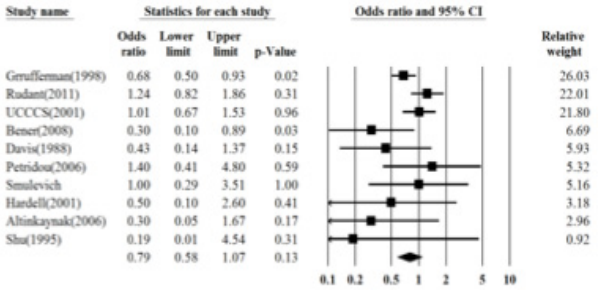

Figure 2. Adjusted Odds Ratios Association between Breastfeeding and the Risk of Childhood Hodgkin Lymphoma. Test for heterogeneity: Q = 14.00; P = 0.12; I^2 = 35.70%. "Never" includes the breastfeeding duration of < 1 month (Hardell et al 2001); 1-2 months (Smulevich et al 1999). For each study, the estimate of OR and its 95% CI is plotted with a box (■) and a horizontal line. The size of a box is proportional to the weight that the study undertakes in calculating the summary effect estimate (◆)

or reported data to calculate these measures.

Data Extraction

From each study we extracted the following data: the first author's last name; year of publication; country or region where the study was performed; age range; estimated year of birth; method of assessing breastfeeding; definitions of breastfeeding; number of cases; number of controls; confounding factors that were adjusted for in the analysis; and the RR or OR estimates with corresponding 95% CIs. We extracted both minimally and maximally adjusted risk estimates of RRs or ORs with 95% CIs for the main analysis. If available, the effect of breastfeeding duration from each study was also extracted. The quality of the study was assessed using the 9-star Newcastle-Ottawa Scale (NOS) (Stang, 2010), the study with 7 or more stars were identified to be higher-quality. Two authors (K.L.W and C.L.L) conducted the data extraction independently and any disagreements were resolved by consensus.

Statistical Analysis

The maximally adjusted RRs or ORs of the associations and 95% CIs were combined using a random effects model to analyze the results. The RRs or ORs with 95% CIs of each study among those breastfeeding compared with those who never breastfed were used as the principal outcome. In the dose-response meta-analysis, we computed the trend between the correlated log RR or OR estimates with categories of the breastfeeding duration using a meta-regression method.

Statistical heterogeneity among studies was evaluated using Q and I^2 statistics. For sensitivity analyses, we repeated our analysis using the fixed-effects model and the minimally adjusted RRs or ORs. The potential publication bias was examined using a funnel plot for asymmetry, and was further quantitatively examined using the Begg's rank correlation test and the Egger's linear regression test. Comprehensive Meta Analysis (v.2.0; Biostat, Englewood, NJ, USA) was used for meta-analysis. A two-sided P value < 0.05 was considered statistically significant.

Results

Literature Search

The detailed steps of the literature search and the selection process are shown in Figure 1. Briefly, 11 potentially relevant articles that concerned the association between breastfeeding and the risk of childhood Hodgkin lymphoma were identified (Davis et al., 1988; Shu et al., 1995; Grufferman et al., 1998; Smulevich et al., 1999; Hardell et al., 2001; UK Childhood Cancer Study Investigators, 2001; Altinkaynak et al., 2006; Petridou et al., 2006; Bener et al., 2008; Rudant et al., 2011). One article was only published in abstract form in 1998 by Grufferman et al. (1998). We excluded 1 article because of duplicate reports from the same study population (Bener et al., 2001).

Study Characteristics

The main characteristics of the 10 studies are as follows, of which 9 were population-based case-control studies and 1 was a hospital-based case-control study. Ten studies were published between 1998 and 2011 and involved 1618 cases and 8181 controls. Five studies were based in Europe, 2 in North America, and 3 in Asia. The age range was between 0 and 17 years and the estimated year of birth was between 1960 and 2004 for all participants. Of the included studies, 5 studies were categorized as higher-quality study and 4 were lower-quality study.

Breastfeeding and the Childhood Hodgkin Lymphoma Risk

Figure 2 shows the results of the multivariable-adjusted OR for each study and combination of all studies for comparing ever breastfeeding with never breastfeeding. The results from studies on the association between breastfeeding and the risk of childhood Hodgkin lymphoma were inconsistent, with both inverse and positive associations. The pooled OR of childhood Hodgkin lymphoma for comparing ever breastfeeding with never breastfeeding was 0.79 (95% CI, 0.58-1.08; P = 0.13). There was limited evidence for heterogeneity across the included studies (P =0.12, I^2 = 35.70%).

A significant decrease in risk of childhood Hodgkin lymphoma associated with breastfeeding was observed in lower-quality studies (OR=0.49; 95% CI, 0.28-0.88)

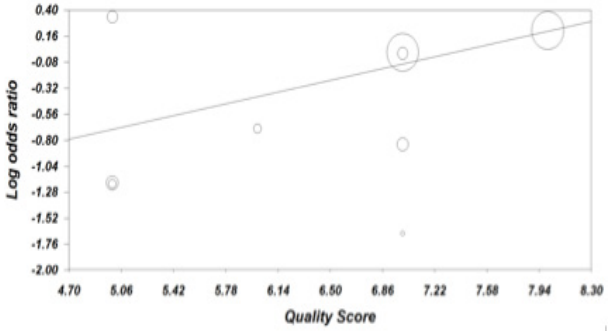

Figure 3. Relationship Between the Study Quality Score and Odds Ratios of Childhood Hodgkin Lymphoma in a Random Meta-regression Model. The meta-regression analysis between study quality score with Log Odds Ratios in 9 studies (Not included the study by Grufferman et al 1998), White circles represent individual study

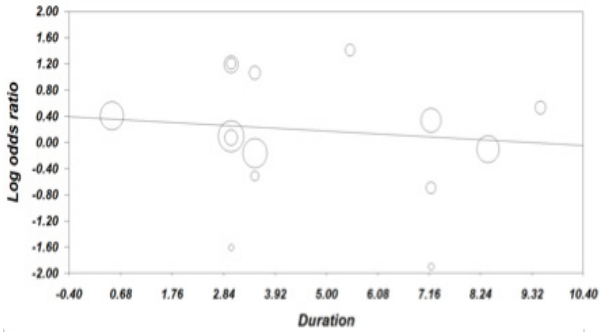

Figure 4. 4 Dose-Response Relationship Between the Breastfeeding Duration and Odds Ratios of Childhood Hodgkin Lymphoma. The breastfeeding duration was modeled with a linear trend in a random-effects meta-regression model. White circles represent individual study

Table 1. Subgroup Analysis

Subgroups	No. of studies	OR (95% CI)	*p* value I^2, %	*P* value for heterogeneity	*P* value for between subgroups
Study quality					0.02
Lower-quality	5	0.49(0.28-0.88)	0.02	0	0.64
Higher-quality	4	1.10(0.83-1.45)	0.52	0	0.42
Region					0
North America	2	0.66(0.49-0.89)	0.01	0	0.46
Asia	3	0.12(0.12-0,70)	0.01	0	0.96
Europe	5	1.10(0.84-1.45)	0.49	0	0.82
Breastfeeding duration					0.43
0-6 months	6	1.03(0.78-1.37)	0.82	0	0.89
>6 months	6	0.80(0.46-1.39)	0.42	28.9	0.22

but not in higher-quality studies (OR=1.10; 95% CI, 0.83-1.45). Furthermore, we noted an increasing trend between the logORs of childhood Hodgkin lymphoma and the study quality scores in nine studies using a random effects meta-regression model (P =0.03, Figure 3). Subgroup analysis by geographic region revealed that breastfeeding had a protective effect on the risk of childhood Hodgkin lymphoma in the North American (OR=0.66; 95% CI, 0.49-0.89) and a stronger protective effect in Asian populations (OR=0.29; 95% CI, 0.12-0.70), but not the European population (OR=1.10; 95% CI, 0.84-1.45) (Table 1). We further conducted a subgroup analyses involving the breastfeeding duration in which comparisons were classified into the following two situations using a random effects model: breastfeeding duration of 0-6 months vs. never breastfeeding; and breastfeeding duration > 6 months vs. never breastfeeding. We found that the pooled OR comparing the breastfeeding duration of 0-6 months with never breastfeeding was 1.03 (95% CI: 0.78-1.37; P = 0.82) and the pooled OR comparing the breastfeeding duration > 6 months with never breastfeeding was 0.80 (95% CI: 0.46-1.39; P = 0.42).

Dose-response meta-analysis of the breastfeeding duration

We next assessed the dose-response relationship between childhood Hodgkin lymphoma and the breastfeeding duration using a meta-regression method (Figure 4). Along with the increase in breastfeeding duration, the point estimates of the effect decreased, but there was no statistical significance ($P_{\text{meta-regression}}$ =0.44).

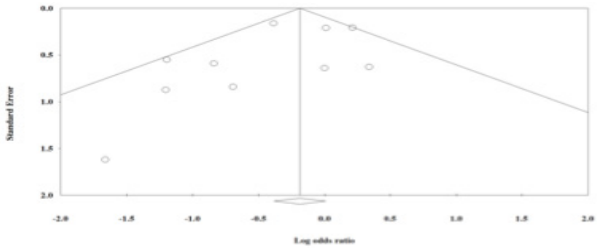

Figure 5. Funnel Plots of Association Between Breastfeeding and the Risk of Childhood Hodgkin Lymphoma. White circles represent individual study and white diamonds represent the pooled estimate from the meta-analysis. The diagonal lines represent the 95% CI of the summarized effect estimate, which is indicated by the vertical line

Sensitivity analyses

A sensitivity analysis by repeating the meta-analyses using a fixed-effect model (OR =0.83, 95% CI: 0.68-1.01; P = 0.06) showed that there was no substantial change in the results. A sensitivity analysis, excluding one study with an abstract form only by Grufferman et al. (1998), accounted for 26% of the relative weight in a random effects model and did not show any substantial change (pooled OR: 0.82; 95% CI: 0.56-1.12; P = 0.29). We further conducted a repetition analysis by using the minimally adjusted effect estimates, but did not find any substantial change in the pooled results.

Publication Bias

The publication bias among studies of childhood Hodgkin lymphoma and the duration of breastfeeding was not appreciable based on funnel plots (Figure 5). P values for Begg's rank correlation test and Egger's regression test were 0.24 and 0.59, which confirmed that there was no clear evidence of publication bias.

Discussion

Our meta-analysis was carried out to evaluate the association between breastfeeding and the risk of childhood Hodgkin lymphoma. Overall, we found that there was no significant association between breastfeeding and the risk of childhood Hodgkin lymphoma.

The association between breastfeeding and the risk of childhood Hodgkin lymphoma has been assessed in a previous meta-analysis of 6 case-control studies (Martin

et al., 2005), which reported a 24% (3-40%) risk reduction of childhood Hodgkin lymphoma associated with ever breastfeeding. Compared to the meta-analysis (Martin et al., 2005), we added 3 new studies (Altinkaynak et al., 2006; Petridou et al., 2006; Rudant et al., 2011) and 1 study by Bener et al. (2008) in 2008 that enlarged the sample size in 2001 (Bener et al., 2001). Notably, the findings from our meta-analysis suggested that there was limited evidence for a significant association between breastfeeding and the risk of childhood Hodgkin lymphoma. The inconsistent finding of our meta-analysis may be driven by the results from a new study which constituted > 50% (843 cases) of all cases (1618 cases) (Rudant et al., 2011). After excluding this single study, we observed a significant inverse association (pooled OR: 0.72; 95% CI: 0.54-0.96; $P = 0.02$).

The anticancer mechanism of breastfeeding remained unclear, which may be a direct effect of human milk on malignances or an indirect effect of reducing early childhood infections (Section on Breastfeeding, 2012). A complex biological liquid containing numerous immunoactive agents might play an important role in the anticancer activity of human breast milk. High levels of human soluble TNF-related apoptosis-inducing ligand were found in human colostrum and breast milk, which is an immunoactive substance that plays a key role in controlling apoptosis and cell proliferation in various organs and tissues (Davanzo et al., 2013). Human alpha-lactalbumin made lethal to tumor cells, which is a substance with anticancer activity in human milk, has been reported (Mossberg et al., 2010).

A significant decrease in risk for childhood Hodgkin lymphoma was observed in five lower-quality studies but not in four higher-quality studies. Our finds are mainly based on the results from higher-quality studies. Subgroup analyses by geographic region revealed that breastfeeding had a prospective effect on childhood Hodgkin lymphoma in North America and Asia for children who have been breastfed, but not in Europe. We further noted that there was a higher risk reduction in Asia (71%) than in North America (34%). In developing countries, children are easier to be infected during early childhood, which was related to childhood Hodgkin lymphoma (Flavell et al., 2000). The different risk reduction of childhood Hodgkin lymphoma between Asia and North America may be partly due to the more remarkable effect of breastfeeding against early infections among Asian children (Swerdlow, 2003; Dinand et al., 2006; Paltiel et al., 2006; Section on Breastfeeding, 2012). Additionally, the small sample size of the three studies from Asia might have influenced the summarized results.

In the subgroup analyses based on breastfeeding duration, we noted that children who were breastfed for > 6 months tended to have a higher risk reduction of childhood Hodgkin lymphoma than those with breastfeeding duration < 6 months, although there were no statistically significant associations in both groups. Of the 9 studies that reported relevant data about different breastfeeding durations, 8 simply divided the breastfeeding duration into the intervals of < 6 months and > 6 months, and only 1 study assessed the effect of > 12 months of breastfeeding (Smulevich et al., 1999), which was still shorter than the breastfeeding duration proposed by the World Health Organization (24 months) (WHO, 2010). We further conducted a meta-regression analysis based on breastfeeding duration and found that the potential protection effect of breastfeeding tended to be stronger, along with the increase in breastfeeding periods, although without statistical significance. In view of the findings above, it could be speculated that the underlying protective effect of breastfeeding against childhood Hodgkin lymphoma may be able to reach a significant level when exposure is for a sufficient period of time. However, this hypothesis should be assessed and confirmed in future studies.

To explore whether or not the characteristics of studies or participants could have affected the summarized results, we conducted meta-regression analyses and found that the between-study heterogeneity was related to the quality score with a marginal significance (P =0.03), but unlikely to be attributed to the following characteristics of the participants or studies: sample size ($P_{\text{meta-regression}}$ =0.32); and publication year ($P_{\text{meta-regression}}$ =0.14). The observed protective effect seemed to be attenuated in studies with higher study quality scores as compared to those with lower scores. In addition, a variety of exposure measurements across the included studies and the varied definitions might have contributed to the heterogeneity.

By pooling all of the available published literature, we estimated whether or not breastfeeding reduced the risk of childhood Hodgkin lymphoma and quantified the dose-response relationship between the duration of breastfeeding and risk of childhood Hodgkin lymphoma using meta-regression analysis. In addition, we compared the results of minimally and maximally adjusted effect estimates and did not note any substantial difference in the pooled results, suggesting that the observed result was unlikely to be affected to the adjusted potential confounding factors in these included studies.

There were some limitations in this meta-analysis. First, all of the current evidence from the included studies was based on observational studies. Second, none of the included studies reported the dosage and frequency of breastfeeding. Another limitation was that the definition of breastfeeding and measurement methods varied across the included studies. Additionally, the residual confounding effects by factors that were not controlled or adjusted among the included studies might have influenced the observed results.

In conclusions, our meta-analysis of 10 studies involving 1618 cases and 8181 controls demonstrated that there is limited evidence for a significant association between breastfeeding and the risk of childhood Hodgkin lymphoma. Given the limited number of related studies and the relative small sample size, further high-quality studies especially cohort studies are needed.

Acknowledgements

The author(s) declare that they have no competing interests.

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