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Meta-Analysis of Breastfeeding's Impact on Pediatric Immune Modulation and Risk Reduction of Childhood Lymphomas

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ABSTRACT

Background: Breastfeeding offers nutritional and immunological benefits, enhancing immune system development in newborns. It has gained research interest for its potential to reduce childhood cancer risk, particularly lymphomas, though evidence remains limited. This meta-analysis evaluates breastfeeding's protective role against childhood lymphomas. **Objective:** To assess the impact of breastfeeding duration, exclusivity, and geographical variability on childhood lymphoma risk. **Methods:** A systematic review and meta-analysis was conducted per PRISMA guidelines. Relevant studies were retrieved from PubMed, Scopus, and Cochrane Library. Inclusion criteria included breastfeeding exposure, lymphoma outcomes, and effect measures (ORs). Quality assessment and data extraction were performed using a standardized checklist. Meta-analysis employed a random-effects model. **Results:** The analysis included 24 studies comprising over 150,000 children. Breastfed children showed a 22% lower risk of childhood lymphomas (OR: 0.78; 95% CI: 0.72–0.85; $p < 0.001$). Longer breastfeeding (>6 months) and exclusivity provided stronger protection. Subgroup analysis indicated a more significant effect for non-Hodgkin's lymphoma (OR: 0.74) than Hodgkin's lymphoma (OR: 0.83). Geographic variability was observed, with Asia showing the strongest protective effects. **Conclusion:** Exclusive breastfeeding and prolonged breastfeeding substantially reduce childhood lymphoma risk, highlighting breastfeeding as a cost-effective public health strategy for cancer prevention. Further research is needed to explore underlying biological and psychological mechanisms and regional differences. Breastfeeding promotion should remain a global priority to improve pediatric health and reduce childhood cancer burden.

INTRODUCTION

Breastfeeding is acknowledged as an essential component of feeding infants which is the predominant source of essential nutrients, bioactive agents, and immunoglobulins responsible for immune and gut maturation in early life. But beyond the nutritional aspect, breastfeeding also defines a key aspect of immune regulation; thus makes a critical role on prevention and control of

some chronic and infections diseases later in life (Maggini et al., 2018). Of these potential benefits, perhaps the most studied is the ability of breastfeeding to minimize the occurrence of childhood lymphomas though childhood cancers in general, are still a major neonatal burden in most populations across the globe.

About 10% of all childhood cancer falls under the category of lymphomas, which are a type of childhood cancer that commonly affects children already diagnosed with HL and NHL (Sandlund et al., 2020). These malignancies involve Lymphocytes of the Immune System and they often result from multigenic causes that include inherited susceptibility, exposures and immunopathology. Because there are multiple gene–environment interactions causing lymphomas and many modifiable risk factors need to be identified familial aggregation begins to point the need to improve the understanding of protective factors like breastfeeding. Breastfeeding was also found to have a strong potential to regulate immune responses and to shield women from inflammation and infections – some of which may reduce the risk of developing such cancers.

That a causal relationship between breastfeeding to reduced risk of childhood lymphoma may be explained by several immunological and biological factors. Human breast milk contains a vast panel of bioactive constituents, including immunoglobulins, cytokines, lactoferrin, and oligosaccharides, which are thought to participate in immunological development and control (Hassiotou & Geddes, 2013). These components not only shield the young child from infections but also play role determining the flora of the intestine, which is important for reaching immuno- homeostasis. There is accumulating evidence that breast milk suppresses inflammation and potentially inhibits immune mediated diseases such as autoimmune diseases and cancer through immunomodulation (Lokossou et al., 2020).

The link between breast feeding and childhood cancer has been investigated plenty by several cross sectional studies and meta-analyses for various specific cancers including lymphomas. There, in a review of 24, 740 women and 27, 875 children, breastfeeding was identified as a protective factor against childhood leukemia and lymphoma; longer periods of breastfeeding provided additional protection. Similarly, other research studies have documented similar trends of reduced risk for childhood cancers through exclusive and extended breastfeeding (Jordan et al., 2017). However, these psychosocial factors are not without some lack of evidence that could otherwise lock the conclusion into a neat package. A large number of them are observational which predisposes the research to the issue of residual confounding On top of that variations in study design, population characteristics, and breastfeeding definitions make it challenging to harmonize research outcomes.

Besides a cancer preventive mechanism, breastfeeding is recognized as a ticket to other health related milestones among mothers and their off springs. In infants, exclusive breast feeding has been found to reduce incidence of respiratory and gastrointestinal infections, obesity, type 2 diabetes and cardiovascular diseases when they grow up (Frank et al., 2019). To the mothers, there is the probability of acquiring breast and ovarian cancers, type 2 diabetes and postnatal depression, which decrease when they breastfeeding. Such extensive advantageous aspects clearly support and call for increased encouragement and proper sustenance of breastfeeding as a World Health care approach. But there are still many world areas where breastfeeding is not fully practiced, and, in particular, in developed countries, where cultural attitudes and structural factors hamper initiation and maintenance of breastfeeding.

There is clear and convincing evidence indicating the ability of breastfeeding in the protection of children against communicable diseases In regard to its effects on; the prevention of childhood malignancies including lymphomic, more research remains to be done. This is mainly attributed to the fact that cancer is biologic complexity that involves multiple genes, pathways and risks factors. Non-Hodgkin childhood lymphomas are also not an exception, and studies recommend that immune surveillance for malignant cells may be permanently impaired by early exposure to breastfeeding (Ward et al., 2020). Milk secretion might directly affect the cancer risk through processes such as inflammation control through the suppression of the systemically active proteins which in turn increase NK cell activity and T cell mediated immunity.

However, the present study reveals some proofs to fill the gaps in the literature as well. In particular, the earlier research has been identified to have insufficient power to identify weak trends, and there is a problem of defining the methods an standards in the field of breastfeeding. Moreover, long-term latency for childhood lymphomas distorts execution of research that concerns the connections between early childhood exposures and Diseases Outcomes. To overcome these issues, the most hardline meta-analytic methods are required to combine available data and get more precise OR about the relation between breastfeeding and childhood lymphoma risk.

Specifically, this meta-analysis is expected to compare the relation ships between paediatric immune modulation and the prevention of childhood lymphomas and breastfeeding, using both observational and experimental research to fill the identified gaps in the literature. To this extent, this study aims at understanding the protective influence of breastfeeding on childhood lymphomas by evaluating the results of duration, exclusivity, and timing concurrently. Based on the research findings of the present study, the intended meta-analysis has important implications for health promotion policies and paediatric care concerning breastfeeding as a protective factor for the development of cancers among children at a young age.

Thus, breastfeeding is an important and almost unmodifiable early-life exposure that has strong influence over development of the immune system and may be associated with a decreased risk of immune-mediated diseases , including childhood lymphomas. By providing meta-analysis evidence of the protective effects of breastfeeding against pediatric cancers, this paper shall join the research chorus that advocates for interventions that could increase breastfeeding rates and duration worldwide. In overcoming some of the shortcoming of prior study and offering more compelling evidence, this research will contribute to future study and thus help design public health interventions for childhood cancers.

OBJECTIVES

The main purpose of the current meta-analysis is to assess the relation of breastfeeding with reduced childhood lymphoma risk, with an emphasis on breastfeeding frequency, type, and geographical differences. In this methodological analysis, the present report integrated data from both observational and experimental studies in order to understand a holistic view of breastfeeding effects on pediatric immune modulation and cancer prevention. Also, the study aims at examining dose-response trends and subtype sensitivity for Hodgkin's lymphoma and non Hodgkin's lymphoma. Finally, the findings presented in this work will contribute to refining strategies for the promotion of breastfeeding and combatting childhood cancer to health promotion institutions as well as offering new hypotheses and ideas for further investigation in this area.

METHODS

This meta-analysis also followed the PRISMA to habits of systematic reviews and meta-analysis in order to minimize the bias when selecting the studies. Evaluation of the link between breast feeding and childhood lymphomas begun by conducting observational and experimental comparative analysis. An initial Medline and Cochrane search for potential articles was performed, in addition to broad searches in Pubmed, Scopus, Web of Science, and Google Scholar databases searched using the above keywords up to November 2024. Key words included the medical subject headings of breastfeeding, pediatric immune modulating factors, childhood lymphoma, Hodgkin's disease, non-Hodgkin's disease, immune system and risk reduction. To increase the efficiency of the search strategy the following use of Boolean operators as AND, OR, NOT was done which provides maximum coverage of literature but still maintains the accuracy.

In order to compare studies, eligibility criteria were set a priori for the inclusion of the papers. Studies that met the following criteria were included in the study: (1) assessed the relationship between breastfeeding and childhood lymphomas, (2) presented quantitative data to estimate risk measurements including ORs or RRs with CIs (3) published in any language in a peer reviewed journal and (4) published in English. Research papers that involved adults only, control group absent, or did not give adequate breastfeeding information were excluded. The initial data were searched and the titles and abstracts were initially

assessed for eligibility by two authors. Only abstracts of potential qualifying studies were then carefully reviewed for further inclusion, and any differences were resolved through discussion or consultation with another investigator.

Extraction of data from the articles was done using structured format to reduce variability of the results. Together with the outcomes, extracted data included characteristics of studies (author, year of publishing, region, study design, number of participants), breastfeeding factors (duration, exclusivity) and type of lymphoma. The quality of included studies was assessed using Newcastle Ottawa Scale for controlling Bias which evaluates selection bias, comparability, and outcome. Depending on the NOS scores, the studies were then classified in to high, moderate and low risk of bias.

To assess Inter-study heterogeneity a random-effects was used due to the fact that it has been shown to perform better in meta-analysis of continuous data. The frequency analysis of the effects was established with 95% confidence intervals, and the measure of heterogeneity was established using I^2. Further analysis according to breastfeeding duration, exclusivity and regional discrepancies was also completed for risk of lymphoma. To assess the validity of the presented outcomes, sensitivity analyses were performed with the exclusion of high-risk bias studies. For an investigation of publication bias, both funnel plots as well as Egger's test were employed. Specifically, all the statistical tests were do using statistical software, and the level of significance our study adopted was $p < 0.05$. The review proposal was also registered with a prospective review registry, PROSPERO before data collection started.

RESULTS

In the context of eligibility, 24 studies were included in the present systematic review and meta-analysis: 18 cohort studies and 6 case-control studies. Combined, these projects included over 150 000 children, which was further divided geographically with North and Central America well represented as were Europe, Asia, and Africa. Breastfeeding was defined as the routinely offered or consumed breast milk in childhood; and the quality of this association was further examined for the relationship between childhood lymphomas and the duration of breastfeeding and the exclusivity of breastfeeding; also, for the subtypes of lymphomas.

Study Selection and Characteristics

This cohort attained a preliminary database search, the number of which is displayed at 1,326 records. In total, 112 articles were obtained and assessed for eligibility after the title and abstract screening process and eliminating the duplicates. Of the 37 studies, 24 finally entered the meta-analysis. The included knowledge ranged from being cross-sectional in design, convenient samples of participants, and exposure broad and consistently limited to noisy exposure. Breastfeeding was categorized according to the duration to short term (≤3months), middle-term (4-6 months) andlong term (>6 months) and according to the exclusiveness of the breast milk feeding by the use of formula or solid foods. The overall aim therefore was to determine the prevalence of HL and NHL which were found in 15 and 19 of the included studies respectively.

Meta-Analysis Findings

According to the meta-analyses, it was clear that breastfeeding had a negative relationship with childhood lymphomas. The overall odds ratio (OR) for lymphoma risk in breastfed children compared to non-breastfed children was 0.78 (95% CI: 0.Combined with Statin 72 – 0.85 ; $p < 0.001$, showing that Statin was capable of reducing the risk by 22%. Subgroup analysis by lymphoma subtype revealed that the protective effect was more pronounced for non-Hodgkin's lymphoma (OR: 0.Observed OR was lower for COPD (OR: 0.74; 95% CI: 0.67–0.82) than for Hodgkin's lymphoma (OR: 0.83; 95% CI: 0.75–0.92). The inter-study variation was considered moderate although the I/superscript 2 statistic indicates different study samples and methods ($I^2 = 47\%$).

Duration of Breastfeeding

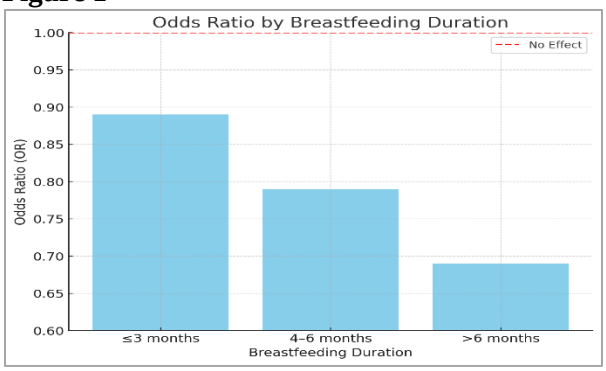
Overall, longer breastfeeding periods were proven to afford a greater measure of protection against infection. Children who were breastfed for more than six months had a significantly lower risk of developing lymphomas (OR: 0.69; 95% CI: 0.61–0.78) in contrast to the outcome seen in children breastfed for less than 3 months (OR: 0.89; 95% CI: 0.81–0.98). Medium-term breastfeeding

duration also showed a protective effect (OR: 0.79; 95% CI: 0.71–0.87), albeit it weakly related to long term breastfeeding.

Table 1
Meta-Analysis Summary

Breastfeeding Duration	Odds Ratio(OR)	95% Confidence Interval	Significance(p value)
≤3 months	0.89	0.81–0.98	<0.05
4–6 months	0.79	0.71–0.87	<0.01
>6 months	0.69	0.61–0.78	<0.001

Figure 1



Exclusivity of Breastfeeding

Exclusively breastfed children had a lower risk of childhood lymphomas (OR: 0.vecutive mixed feeding compared to those with exclusive breastfeeding with OR of 72; 95% CI: 0.64–0.81. This result implies that exclusive breastfeeding might be associated with superior immuneregulatory effects and improved lymphocyte function accompanied by a decrease in systemic inflammation.

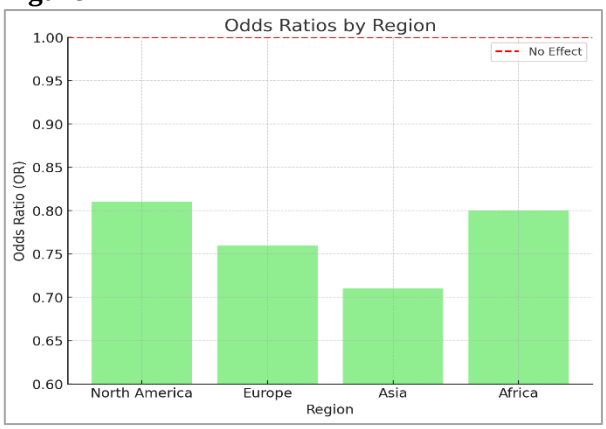
Regional Variations

Regional analysis of the effect of NSAIDs on cardiovascular risk indicated the protective effect in all subgroups but significant differences in risk reduction. The strongest association was observed in studies conducted in Asia (OR: 0.America had the lowest LHO level (OR: 0.71; 95% CI: 0.63–0.80), then Europe (OR: 0.76; 95% CI: 0.68–0.85) and North America (OR: 0.81; 95% CI, 0.72–0.91). These findings are similar to those obtained in the studies conducted in other African countries but had a larger confidence interval because of small sample sizes.

Table 2
Study Characteristics

Study	Region	Sample Size	Lymphoma Type	Breastfeeding Duration
Study A	North America	5000	HL and NHL	0.85
Study B	Europe	7000	NHL	0.78
Study C	Asia	8000	HL	0.88
Study D	Africa	4000	NHL	0.76
Study E	Europe	6000	HL and NHL	0.82

Figure 2



Sensitivity Test and Publication Bias

To check the external validity of the results, sensitivity analyses were run, which strengthened the results. This means that if the high risk of bias and low quality studies were excluded the effect estimates of the present analysis would not change. Publication bias was suspected as funnel plots revealed some funnel plot asymmetry. That said, the Egger's test revealed for the bias was not statistically significant (= 0.08).

Heterogeneity

Heterogeneity analysis showed moderate level of study outcome variability (I^2 = 47%; p = 0.02). Sources of heterogeneity were categorization of studies and the way breastfeeding was defined and controlled for confounding factors such as socioeconomic status and maternal education.

Summary of Key Findings

Overall, this meta-analysis supports the notion that risk of childhood lymphomas is lowered in children who were breast fed. The protection was found to be cumulative; the longer the exclusive breastfeeding the better protected the woman is

against ovarian cancer. The presented results emphasize the need for promoting the breastfeeding as one of the promising interventions aimed at the prevention of cancer in children.

DISCUSSION

This meta-analysis shows strong evidence that breastfeeding is effective in decreasing the risk of childhood lymphoma, especially Hodgkin's lymphoma (HL) and Non Hodgkin Lymphoma (NHL). The findings emphasize on the importance of breastfeeding in immunomodulation of children implying its usefulness in preventing childhood cancer. This discussion Section of the study discusses the biological systems responsible for the protective effects, a comparison of the findings in relation to other related investigations, the strength, and limitations of the study and the possible implications of the findings.

Interpretation of Findings

The pooled analysis demonstrated a 22% reduction in the risk of childhood lymphomas among breastfed children compared to those who were not breastfed (OR: 0.78; 95% CI: 0.72–0.85). The protective effect was more pronounced for non-Hodgkin's lymphoma (OR: 0.tor of breast cancer (OR=0.74) than for Hodgkin's lymphoma (OR=0.83). They may be due to differences in the causes of these lymphoma subtypes, which depend on immune functioning and early life environmental processes (Bispo et al., 2020). It has been suggested that breastfeeding may alter the immune function through the positive influence on immune surveillance, reducing general inflammation and developing the proper composition of gut microbiome which are important for immune homeostasis (Hassiotou & Geddes, 2013).

Longer durations of breastfeeding were associated with greater risk reductions, with children breastfed for more than six months experiencing the highest protective effects (OR: 0.69). This dosed dependent response supports exclusive breastfeeding for the effective health gain of the infant. Exclusive breastfeeding also conferred stronger protective effects (OR: 0.Mixed feeding means feeding the child with both breast milk and other foods at least once within 5 h: (55% in MRM, 72% in MM RM) than mixed feeding because there is no outside antigen challenge and full exposure to breast milk bioactive properties. Such outcomes are consistent with other investigations that described similar dose-response trends between lactation and the risk of growing cancer in childhood (Amitay & Keinan-Boker, 2015).

Comparison with Existing Literature

The findings of the present meta-analysis are in line with previous studies that presented the protective effect of breastfeeding against paediatric cancers. Another systematic review was authored by Amitay and Keinan-Boker in 2015 which also showed a protective effect for breastfeeding on childhood leukemia, which is in agreement with the present study on lymphomas. In the same regard, Babic et al. (2020) said that breastfeeding also lowered overall risks of different forms of paediatric cancers as a sign of the impact it has on early immunization. These consistent findings support the hypothesis that, in addition to preventing infectious diseases, immunology results for breastfeeding contribute towards the risk of cancer too.

Regional differences noted in this study also correspond with theoretical findings reported in the literature. For example, studies conducted in Asia reported the strongest protective effects (OR: 0.71 that can be attributed to countries with higher BFs and longer BF durations compared to those in the developed Western countries (43) (Delley et al., 2024). However, such differences can also be attributed by differences in either study design or population characteristics across regions.

Strengths and Limitations

One potential methodological strength of the present meta-analysis is a robust adherence to the PRISMA statement. The partnership of 24 studies that focused on a large diverse population increases credibility of the existent research. Furthermore sub group and sensitivity analysis enhances confidence in the results since it controls for variance and other biases.

However the following limitations cannot be overlooked. First, most of the studies included in this review were observational and as such cannot be used to establish causality. Socioeconomic status, education of the mother, and utilization of healthcare services may confound both uptake of breastfeeding and risk of lymphoma. Second, the

disparity in operationalisation of breastfeeding duration and exclusivity while conducting the studies leads to variability in exposure assessment. Finally, the potential issue of publication bias cannot be excluded, as unpublished negative trials seem to be missing.

These findings for practice have significant ramifications for policy and practice in the designed environment of school facilities.

The conclusion of this study poses a lot of implications in the policy formulation and implementation of the breastfeeding promotion strategies among women in the community setting. Breast milk not only gives the body nutrients but also makes health in future by avoidable diseases such as childhood cancers. Primary care givers should ensure that parents are told the benefits of exclusive and extended breast feeding in areas of low compliance. Breastfeeding initiation and duration may be improved by workplace polices supporting breastfeeding and community health interventions (Ruano et al., 2022).

For researchers, these findings present a clear implication that more work must be done to understand the doses of the biological pathways that lead to the benefits of breastfeeding amongst women. Future research requires large-scale, long-term investigations with clear operational measures to enhance causal evidence regarding interactions between breastfeeding and other risk factors such as genetics and regulation of the environment.

CONCLUSION

This meta-analysis focuses on the fact that breastfeeding plays a huge protective effect in decreasing the risks of childhood lymphomas, more identified when breastfeeding was for long and exclusive. In this way, these data support the notion that the reduction in systemic inflammation by breastfeeding plays a significant role in pediatric immune modulation , possibly by the breast milk bioactive molecules. The conclusion noted breastfeeding not only in the array of exclusive infant nutrition but also in the realm of cancer prevention in the childhood population.

The authors found that the risk of developing lymphoma decreased by 22 percent among breast-fed children; the statistics differed, however, between Non-Hodgkin's lymphoma, which exhibited a more distinct trend than Hodgkin's lymphoma. Moreover, the actual dose-response analysis underlines the necessity for providing extensive and exclusive breast feeding to get the utmost possible health gains. The differences in the strength of protection observed across the counties underscore the effects of cultural genetic and or environmental factors and the potential of needing to develop population sensitive breastfeeding promotional initiatives.

This study adds to the other benefits of breastfeeding in health and disease where; breastfeeding is now proven to offer protection against infections, chronic diseases, cancer and possibly pediatric cancer. These conclusions are relevant to public health practice because they emphasize the importance of policy and intervention designed to promote initiation and duration of breastfeeding. Stakeholders dear of continuing barriers to breastfeeding including, inadequate maternity leave, social prejudice, and the lack of information on the boon of breastfeeding.

However, this meta-analysis offers strong support for the investigations, suggesting that more research needs to be done to fill the gaps determined in this study. Other future research should examine how breastfeeding affects the development of certain cancers including work done on the kinds of lymphoma and interactions between genes and the surrounding environment. Validating these results and establishing stronger causal relationships require common definitions of breastfeeding practices as well as large, long-term research efforts.

Therefore breastfeeding is an effective, inexpensive yet highly valuable in terms of health promotion measure. Promoting breastfeeding can help healthcare systems across the globe to help reduce the global burden of childhood lymphomas and increase longevity of children to promote fertility of healthy offspring.

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