



Original research article

Association of maternal and index child's diet with subsequent leukemia risk: A systematic review and meta analysis



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ARTICLE INFO

Article history:

Received 4 August 2016

Received in revised form 5 January 2017

Accepted 7 January 2017

Available online 25 January 2017

Keywords:

Preconception

Maternal diet

Childhood diet

Food group

Micronutrients

Supplements

Folic acid

Iron

Vitamins

Leukemia

ABSTRACT

Background: Exploring the effect of maternal and/or childhood diet on offspring leukemogenesis is challenging, given differences in food group categories, their potentially variable impact depending on time window of exposure and the multiple leukemia subtypes. We opted to quantitatively synthesize published data on the association of maternal/child diet with leukemia risk.

Methods: Medline was searched until June 30th, 2016 for eligible articles on the association of childhood leukemia with consumption of (i) food groups, excluding alcoholic and non-alcoholic beverages, and (ii) specific dietary supplements before/during index pregnancy and childhood.

Results: Eighteen studies of case-control design (N = 11,720 cases/18,721 controls) were included, of which nine assessed maternal dietary components, five index child's and four both, mainly focusing on acute lymphoblastic leukemia (ALL). Statistically significant inverse estimates for ALL were found (2 studies, 413 cases, 490 controls) for fruit (OR: 0.81, 95% CI: 0.67, 0.99); vegetables (OR: 0.51, 95% CI: 0.28, 0.94); legumes (OR: 0.76, 95% CI: 0.62, 0.94); fish (OR: 0.27, 95% CI: 0.14, 0.53, among the 0–4 year old; 2 studies 215 cases, 215 controls); preconception folic acid supplementation (OR: 0.69, 95% CI: 0.50–0.95; published meta analysis plus 2 studies, 3511 cases, 6816 controls); and use of vitamins during pregnancy (OR: 0.81, 95% CI: 0.74–0.88; published meta analysis plus one study, 5967 cases, 8876 controls). The associations (2 studies) of the remaining food groups and maternal dietary supplements consumption during pregnancy as well as of childhood diet and supplements intake (2–4 studies) were non significant. **Conclusions:** Maternal consumption of specific food groups comprising "healthy" items of the Mediterranean diet, preconception use of folic acid and intake of vitamins during pregnancy were associated with decreased ALL risk. Further research is needed, however preferably with homogeneous dietary information and data on immunophenotypic/cytogenetic subtypes to also explore the interaction of specific macro- and micronutrients intake with gene polymorphisms.

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1. Introduction

The incidence of childhood leukemia (CL) in developed countries is increasing [1]; yet, its etiology remains largely unknown, except for few established associations with rare genetic syndromes and exposure to ionizing radiation [2]. During the last decades, intensive research has been undertaken on the role of environmental, lifestyle and perinatal factors on leukemogenesis risk; consistent findings have emerged regarding potentially new risk factors including high birth weight [3,4], gene polymorphisms as proxy measures of immune modulatory exposures early in life and genetic susceptibility conferred by variation in genes involved in the immune system [5,6].

The early rise of the majority of chromosomal aberrations characterising CL during fetal hematopoiesis [7] and the peak 2–5 years of the age incidence of the more frequent disease subtype, namely acute lymphoblastic leukemia (ALL) [8], reflect the potential association of prenatal and early life environmental exposures with subsequent development of the disease. The findings of a recent meta analysis [9] on the inverse association of maternal prenatal intake of vitamin and folic acid supplements with disease onset are likely to support the hypothesis that maternal diet could, at least, modify the risk of childhood leukemia.

Diet has been strongly associated with the etiology of several solid tumors [10,11] and leukemia among adults [12]. Previous studies have also implied the role of maternal dietary habits before and during pregnancy as well as of childhood diet in the early years of life in the pathogenesis of childhood leukemia [13]; the findings have been, however, equivocal [14,15]. In particular, some publications focused on overall leukemia diagnosis [16–19], others on specific subtypes, namely ALL and acute myeloid leukemia (AML) [13–15,20], and variable age groups, such as disease onset in infancy [21] or early childhood [15]. Among the food groups investigated, several researchers focused on foods containing N-nitroso precursors [17,18,22], a possible carcinogen [23], or on the role of naturally derived DNA topoisomerase II (DNAT2) inhibitors [24]. Lastly, the majority of studies treated maternal or childhood diet consumption as a categorical, whereas others as a continuous variable [14,15,20,21].

In view of lack of consistency regarding the impact imparted by diet and supplements intake on childhood leukemogenesis risk,

we opted to systematically review and quantitatively synthesize results from published literature on this association focusing on: 1. Maternal dietary intake around the time of pregnancy (excluding alcoholic and non-alcoholic beverages), 2. Maternal intake of dietary supplements around the time of pregnancy, 3. Child's dietary intake (excluding breast feeding) and 4. Child's dietary intake of supplements.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25] and in line with an *a priori* protocol agreed and signed by authors. Details on the systematic review process are available in Supplementary material.

2.1. Search strategy for the identification of eligible studies

Eligible studies were sought in PubMed without any restriction in language or study design; end-of-search date was 2016, June 30th. Reference lists of reviews and eligible studies were systematically hand searched for additional eligible studies (“snowball” procedure). Thereafter, study authors were contacted for methodological clarifications, whereas missing or recalculated data were requested.

If multiple publications using the same population were identified (overlapping studies), only the study of larger size or the most recent one was included. Two authors (EN and AAD) working independently and blindly to each other performed the selection of eligible studies; in case of disagreement, final decision was reached by consensus.

2.2. Study eligibility

Eligible were studies examining the association of maternal dietary habits and intake of dietary supplements during pre-conception/pregnancy, as well as childhood nutrition and intake of dietary supplements history before disease diagnosis with risk for CL (ALL, AML or overall leukemia, with “overall” denoting studies treating CL as one homogenous entity without distinction by major subtype). Case series, case reports, *in vitro* and animal studies were

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