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Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis

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ABSTRACT

Objective: To systematically review studies and meta-analyze the literature on the association of maternal and/or index child's coffee, tea, and cola consumption with subsequent development of childhood leukemia and its major subtypes.
Methods: Eligible studies were identified through a detailed algorithm and hand-search of eligible articles' references; thereafter, summary-effect estimates were calculated by leukemia subtype and dose-response meta-analyses were performed.
Results: Twelve case-control studies, comprising a total of 3649 cases and 5705 controls, were included. High maternal coffee consumption was positively associated with acute lymphoblastic leukemia (ALL; OR: 1.43, 95%CI: 1.22-1.68) and acute myeloid leukemia (AML; OR: 2.52, 95%CI: 1.59-3.57). Any or low to moderate maternal cola consumption was also positively associated with overall leukemia (AL) and ALL, A linear trend between coffee and cola consumption and childhood leukemia was observed in the dose-response analyses. On the contrary, low to moderate tea consumption was inversely associated with AL (OR: 0.85, 95%CI: 0.75-0.97), although the trend was non-significant. A null association between offspring's cola consumption and leukemia was noted.
Conclusions: Our findings confirm the detrimental association between maternal coffee consumption and childhood leukemia risk and provide indications for a similar role of maternal cola intake. In contrast, an inverse association with tea was found, implying that other micronutrients contained in this beverage could potentially counterbalance the deleterious effects of caffeine. Further research should focus on the intake of specific micronutrients, different types of coffee and tea, specific immunophenotypes of the disease, and the modifying effect of genetic polymorphisms.

Contents

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1. Introduction

Childhood acute leukemia (AL) has seen a gradual increase in its prevalence during the last decades [1,2]. The pathogenetic mechanisms of the disease, however, with the exception of *in utero* exposure to ionizing radiation [3] and certain drugs and chemicals [4], remain obscure.

A growing body of research, in the field of Nutritional Epidemiology, is directed towards the investigation of dietary habits in relation to solid cancers and leukemia [5]; at the same time, in vitro studies try to elucidate the carcinogenic role of various micronutrients at the cellular level. As the triggering events for childhood leukemia are thought to occur *in utero,* during the critical period of fetal hematopoiesis [6] and the fetus can potentially be exposed thought the placenta to several micronutrients, obtained by the mother through diet, dietary habits during pregnancy merit special consideration in regard to their role in childhood leukemogenesis. Of note are the results from a study on maternal folate supplementation during pregnancy that demonstrated a reduction in the risk of acute lymphoblastic leukemia (ALL) [7], encouraging thus potential interventions on maternal diet.

Coffee, tea and caffeinated beverages consumption, in general has been associated both positively and inversely, with various solid cancers in adults [8]. In this context, the interest has been recently expanded to maternal coffee consumption in relation to childhood AL [9–15]

The available case-control studies, however, are characterized by great heterogeneity, in terms of methodology, types of leukemia studied -namely total AL, ALL, acute myeloid leukemia (AML) or infant leukemia-, sample size, statistical analysis and control for potential confounding factors. Data on maternal tea [9,11–13,15] and cola beverages [9,16] consumption during pregnancy are scarcer, whereas a few studies have investigated childhood cola beverages consumption in the first years of life in relation to childhood AL [16–18].

The possible pathogenetic mechanisms proposed by the different authors attribute the results to an array of micronutrients found in different beverages, their metabolic products, gene interactions or to confounding. Therefore, the heterogeneity of the studies, in combination with their equivocal results, necessitates a more systematic approach.

Taking upon a recent meta-analysis on maternal coffee consumption in association with leukemia [19], we sought to explore the potential effect of other beverages containing caffeine, namely tea and cola beverages on childhood leukemia risk in comparison with coffee, by synthesizing studies reporting on maternal or childhood consumption of these beverages in association with childhood leukemia, as well as its major subtypes, namely ALL and AML.

2. Material and methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20] and in line with an *a priori* protocol agreed and signed by all authors, with respect to the role of maternal or childhood caffeinated beverages intake on the risk of childhood AL.

2.1. Search Strategy for the Identification of Eligible Studies

Eligible studies were sought in PubMed without any restriction pertaining to language or study design; end-of-search date was June 30, 2015. The following search algorithm was used: *((nutrition OR nutritional OR diet OR dietary OR eating OR nutrient OR nutrients OR food OR supplement OR supplements OR ((vitamin OR vitamins OR carbohydrates OR carbohydrate OR protein OR proteins OR fat OR fats OR minerals OR flavonoids OR flavonoid OR cereal* OR sugar* OR nut OR nuts OR vegetable* OR fruit OR fruits OR meat* OR fish OR milk OR pulses) AND (intake OR consumption OR content OR use))) OR (breastfeeding OR "breast feeding" OR breastfed OR "breast fed" OR lactation OR lactating OR "infant feeding" OR "milk feeding")) AND (infants OR infancy OR children OR childhood OR offspring OR pregnancy OR maternal OR mother OR pregnant) AND (leukemia OR lymphoma OR hodgkin OR histiocytosis OR ((lymphoid OR myeloid OR hematologic OR hematopoietic OR haematologic OR haematopoietic OR blood) AND (malignancy OR malignant OR neoplasia OR neoplasm OR neoplasms OR cancer OR carcinogenesis))).* Reference lists of relevant reviews and eligible studies were systematically searched for additional eligible studies in a "snowball" procedure. Study authors were contacted for methodological clarifications and missing or recalculated data were requested. If an author had not responded, a reminder was sent after one week and other means of contact were secondarily used whenever available (telephone, fax).

2.2. Study eligibility

Eligible articles included observational studies (case-control or cohort studies) examining the association between maternal or childhood caffeinated beverages and childhood AL (ALL, AML, or overall leukemia, with "overall" denoting studies treating childhood AL as one homogenous entity without making distinction by major subtype). Case series and case reports, in vitro and animal studies, were excluded.

If multiple publications using the same cohort were identified (overlapping studies), only the study of larger size or the most recent one was included, although information from all relevant publications was retained. Two authors (EN and AAD) working independently and blindly to each other performed the selection of

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