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Maternal anemia and the risk of childhood cancer: A population-based cohort study in Taiwan

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Abbreviations

HR: Hazard Ratio

CI: Confidence Interval

ICD: International Classification of Disease

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

Abstract

Background: Childhood cancer may be related to maternal health in pregnancy. Maternal anemia is a common condition in pregnancy, especially in low-income countries, but the association between maternal anemia and childhood cancer has not been studied using a nationally representative population.

Objective: To examine the potential relation between maternal anemia during pregnancy and childhood cancers in a population-based cohort study in Taiwan.

Methods: We examined the relationship between maternal anemia and childhood cancer in Taiwan (N= 2160 cancer cases, 2,076,877 non-cases). Cases were taken from the National Cancer Registry, and non-cases were selected from national records. Using national health registries, we obtained maternal anemia diagnoses. We estimated the risks for childhood cancers using Cox proportional hazard analysis.

Results: There was an increased risk of cancers in children born to mothers with nutritional anemia (Hazard Ratio (HR): 1.32, 95% CI 0.99, 1.76). Iron deficiency anemia (HR: 1.30, 95% CI 0.97-1.75) carried an increased risk, while non-nutritional anemias were not associated with childhood cancer risk.

Conclusion: Our results provide additional support for screening for anemia during pregnancy. Adequate nutrition and vitamin supplementation may help to prevent some childhood cancer cases.

Introduction

Anemia is a condition characterized by decreased hemoglobin concentration, resulting in the reduced oxygen-carrying capacity of the blood. Anemia in pregnancy can be physiologic due to increased plasma volume relative to cell mass. It can also be pathologic due to folate and iron deficiency, vitamin deficiency, hemoglobinopathies, chronic infections, chronic diseases, or malignancies.[1]

Due to physiologic anemia, anemia in pregnancy is defined using a lesser threshold of hemoglobin levels than in the general population. The Centers for Disease Control and Prevention (CDC) defines anemia in pregnancy as hemoglobin (Hb) levels <11.0g/dL in the first and third trimester of pregnancy and <10.5 g/dL in the second trimester.[2] Anemia in pregnancy is common due to the increased dietary needs of the mother and fetus. On average, a woman requires a daily intake of 400μg folate, 2.20μg of vitamin B12, and 12mg of iron per day, but this requirement increases in pregnancy to a daily intake of 400μg folate, 2.60 μg of vitamin B12, and 27mg of iron per day.[3,4]

The global prevalence of anemia during pregnancy is 41.8%.[5] Severe anemia in pregnancy can affect the fetus by causing impaired oxygenation of the developing fetal organ, inadequate nutrient absorption, impaired brain development, and red blood cell formation.[6] Other adverse birth outcomes associated with anemia in pregnancy include low birth weight, preterm deliveries, high placenta-birthweight ratio, spontaneous abortions, and fetal death.[1,7]

Research suggests that anemia may be related to some cancer in adults. For example, hypoxia induced by iron deficiency anemia is related to cancer formation and metastasis. A cohort study in Taiwan observed an association between iron deficiency anemia and increased risk of pancreatic, liver, kidney, and bladder cancer.[8] Two other studies also showed an increased risk of gastrointestinal malignancy in adults with iron deficiency anemia compared to persons with normal serum iron and hemoglobin levels.[9,10] Also, folate deficiency changes gene expression through DNA hypomethylation and can increase the risk of carcinogenesis.[11]

Cancer is the second leading cause of mortality in children in high-income countries, including Taiwan. Although the etiology of childhood cancers is mainly unknown, known risk indicators include low or high birth weight, older parental age, congenital disabilities, genetic syndromes, and ionizing radiation.[12-14]

Although there are limited studies with conflicting results, some studies on childhood cancer etiology have shown some association between maternal anemia and some childhood cancers,[15] including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and acute myeloid leukemia, although not in all studies.[16-24] Neuroblastoma showed mixed results.[25-28] The relationship between maternal anemia and childhood cancer reported in most studies were mainly incidental findings when investigating a variety of potential causes of childhood cancer; hence the subject was not examined extensively among the multiple gestational exposures, and few papers focused on anemia subtypes. Also, most of the studies relied on the mother’s self-report of having anemia in pregnancy, and studies did not compare nutritional and non-nutritional anemias. Therefore, the present study aimed to examine the relationship between maternal anemia during pregnancy and childhood cancers using objective data from a population-based study in Taiwan.

Methods

Data sources

This study linked multiple health registries together, as previously described.[29] Nearly all residents (99.9%) of Taiwan receive health care coverage through a national healthcare program that began in 1995, under which pregnant women are allowed ten prenatal care visits or more as needed; all healthcare including prescribed medications are free. Information about each health care visit (including date of visit, ICD-9 diagnoses, pharmaceutical treatments, and other information) is recorded in the Registry for Beneficiaries of the National Health Insurance Research Database. The Taiwan Maternal and Child Health Database (births 2004-2014) linked the Registry for Beneficiaries of the National Health Insurance Research Database to the Taiwanese Birth Notification and the Death Registry. This database linked children to their parents through unique identifiers. A flowchart giving details about the inclusion of study subjects is shown in Supplementary Figure 1.

Data Management [Exposure, Outcome, and Covariates]

We also linked the Maternal and Child Health Database to the Cancer Registry (diagnoses 2004 -2015) to identify children diagnosed with cancer (outcome variable). The current analysis includes 2,160 cancer cases diagnosed before age 11 and 2,076,877 non-cases. The Health and Welfare Data Science Center provided all data. Maternal anemia (exposure variable) was determined using ICD-9 codes for the different types of anemia (Supplemental Table S1). Cancer incidence for each year of diagnosis by tumor type, sex, and age are in Supplementary table S2.

The choice of variables as covariates in the model was guided by the literature and by associations observed in the cohort.[12,13,29] We adjusted for the child's place of birth, maternal age, and parity in the final model. Pregnancy smoking and alcohol use are low in Taiwan;[30] similarly, smoking and alcohol use was very low in the mothers in our sample (<2%). Therefore, adjustment for these factors did not change our results. We attempted adjustment for socioeconomic factors (family income and employment status) but these did not change results, and were left out of the final model. These factors were not independently associated with cancer in our sample.[29]

Statistical & Sensitivity Analysis

We estimated the risk of multiple pediatric cancer types using Cox proportional hazard modeling to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). The Cox proportional hazard assumption was met. We additionally conducted sensitivity analyses to examine the relationship between maternal anemia and childhood cancers, stratified by anemia type. We used SAS 9.4 (SAS Institute, Cary, NC) for all analyses.

Ethics and Approval

The study was approved by the Human Subjects Protection boards of the University of California, Los Angeles (IRB#13-001904), Columbia University, the University of North Texas (IRB-21-469), and the Taipei City Hospital Research Ethics Committee

(TCHIRB-10703105-E). This study used existing data, and a waiver of informed consent was received.

Results

Table 1 shows the frequency distribution of childhood cancer cases and non-cases born in Taiwan between 2004 to 2014 whose mothers had anemia in pregnancy by sociodemographic and gestational variables; more information is provided in Supplementary Table 2. There is a slight variation in the percentage distribution of non-cases in urban/rural residences and parity between cases and non-cases. Our earlier study on this cohort describes the variation in cancer types.[29] An earlier publication from Taiwan describes the ages at diagnosis among cancers across childhood and adolescence.[31]

Table 2 shows the relative risk for childhood cancers in children born to mothers with anemia in pregnancy. Children born to mothers with nutritional anemia during pregnancy had 1.32 times the increased risk of childhood cancer. In addition, there was an increased risk of all leukemias in children of mothers with anemia, with wide confidence intervals.

While point estimates for several childhood cancer types were elevated with nutritional anemia and iron deficiency anemia, increases were not seen with non-nutritional anemias.

Discussion

Using data from the Taiwanese national registries, we aimed to determine the association between maternal anemia and childhood cancers. Our results suggest an overall increased risk of childhood cancer in offspring of women with nutritional anemia in pregnancy. We observed elevated point estimates with leukemias, although sample sizes were limited, leading to wide confidence intervals. Although anemias such as Fanconi's anemia and aplastic anemia are linked with some childhood cancers,[32] these did not explain the results.

Prior studies did not stratify by anemia type but observed associations between any type of anemia and risk for childhood cancer. Our result was consistent with some of the studies that previously found associations between maternal anemia and childhood cancers, including leukemia.[17-19] Still, other studies suggested that associations were present only among children diagnosed with leukemia at younger ages,[16,19] an association we were unable to confirm due to limited sample size. A study that reported no relationship between maternal anemia and childhood cancers mentioned that the lack of association may have been due to inaccurate self-reporting of anemia.[22] In our study, we used medically diagnosed cases of anemia to avoid this bias and improve validity.

Worldwide, pregnant women have an increased prevalence of nutritional anemia, especially iron-deficiency anemia. In North America, the prevalence ranges from 7.3% in the first trimester to 32.9% in the third trimester.[33] In our study population, the prevalence of maternal anemia was 6.4%, lower than the 10.8% prevalence of anemia in pregnancy reported in a study using a national database in Taiwan.[34] The lower prevalence in our study may be due to underreporting in the medical record.

In Taiwan, pregnant women are screened for anemia via a complete blood count and one free routine test for anemia in women is typically done at the 12th week of pregnancy.[35] In 2021 (after the current study period), a new policy was made to add another test at 24-28 weeks of pregnancy. Hence, those who developed anemia in the later stages of pregnancy would have been underreported in our study.

The prevalence of gestational anemia increases as pregnancy progresses;[35,36] anemia in early pregnancy has been linked to nutritional deficiency and leads to poor fetal outcomes such as low birth weight.[37] While previous studies have linked low birth weight to increased childhood cancer risk, two cancers often linked to low birth weight, hepatoblastoma and neuroblastoma were not associated with anemia in our study.[29,38] In addition, our study found associations between ALL and anemia, and ALL is a cancer related to high birth weight.[39] Thus, low birth weight does not explain our associations.

Anemia and iron deficiency can increase oxidative stress, cause DNA damage, and DNA mismatch repair genes which may lead to increased risk of carcinogenesis.[40] Iron deficiency impairs heme production and therefore leads to an imbalance in iron-containing mitochondrial enzymes, leading to DNA damage, mitochondrial decay, impaired apoptosis, and potentially carcinogenesis.[40,41] Also, iron deficiency is likely to be associated with the lack of several other nutrients or a pattern of undernutrition, and these factors may act synergistically to promote cancer. Maternal dietary factors in pregnancy, such as the consumption of fruits, vegetables, and protein which are sources of vitamin B12, are understudied in childhood cancer but have been reported to be protective.[42] Most often studied has been leukemia, for which studies have observed a reduced risk with maternal consumption of fruits, proteins, legumes, milk, and dairy.[42-44]

In contrast, foods that have high iron, such as cured meats and smoked fish, have been linked to an increased risk of leukemia.[44] Similarly, taking vitamin supplements during pregnancy has been reported to be protective against childhood cancer.[45-47] The prevalence of anemia due to iron deficiency, folate, and vitamin B12 deficiency in Taiwan is not widely known, but a previous study reported the prevalence of anemia among adult women in Taiwan to be 19.5%, while the prevalence of iron deficiency anemia was 6.2%.[48]

When the type of nutritional anemia was identified in our study, it was identified as iron-deficiency anemia, with no folate or B12 deficiency anemia reported. Hence, the absence of people with folate or B12 deficiency anemia may be due to misdiagnosis or due to lack of testing for folate and B12 deficiency. A 2008 study in Taipei reported low awareness of and use of folate supplementation in pregnancy, with only 15% of women taking supplements.[49] The National Health Administration's nutritional status tracking survey of pregnant women showed that 98% of pregnant women in the third trimester did not meet the standard folic acid intake, and 90% of pregnant women did not meet the recommended intake for vitamin B12.[50] Thus, we cannot be certain that iron deficiency alone is responsible for our findings. Adequate folate supplementation is needed to synthesize DNA of good quality and may be protective against cancers such as leukemia.[51] Folate plays a pivotal role in the formation of S-adenosylmethionine, which is a universal methyl donor in the formation of purine and thymidine, which are essential building blocks for DNA and

RNA. The deficiency of folate may cause alteration in DNA methylation and disrupt the integrity, stability, and repair of DNA. These may enhance cancer development by altering the expression of important tumor suppressor genes and proto-oncogenes.[52] Ecologic studies suggest that folate supplementation in cereal grains reduces the incidence of childhood cancers, including leukemias, neuroblastoma, germ cell tumor, brain tumor, and Wilms tumor.[53,54]

One strength of our study is that our analysis was a population-based cohort study with medical histories from national patient registers, limiting selection bias. Additionally, the use of medical records avoided differential or non-differential maternal recall errors, although not non-differential misclassification due to errors in record keeping. Because childhood cancers are rare, a limitation of our study was the small sample sizes of cancer types. Although the Taiwanese database included information on every medical visit, we lacked information on maternal diet or the use of over-the-counter supplements among mothers. Mothers diagnosed with anemia may have also used supplements to help with their treatment for the anemia, but we do not have access to this information. A study in the UK reported associations between mothers who used iron supplements in pregnancy and the risk of medulloblastoma and Wilms tumor in the offspring,[55] indicating that iron supplement use may play a role. Another limitation is that we did not have details on retesting for improvement in anemia after diagnosis.

In conclusion, the use of nutritional supplements in pregnancy has been shown to reduce the risk of maternal anemia. If results are corroborated elsewhere, this might potentially be beneficial in preventing pediatric cancers.

Conflict of interest statement

The authors report no conflict of interest.

Acknowledgments

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