

Risk Factors of Childhood Cancer in Armenia: A Case-Control Study

**Master of Public Health Integrating Experience Project
Professional Publication Framework**

by

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Yerevan, Armenia
2020

Table of Contents

<i>List of Abbreviations</i>	4
<i>Acknowledgement</i>	5
<i>Abstract</i>	6
1. Introduction	7
1.1 Background	7
1.2 Disease burden	7
1.3 Risk Factors	8
1.3.1 Demographic factors	8
1.3.2 Environmental factors.....	9
1.3.3 Intrinsic factors.....	10
1.3.4 Genetic factors.....	11
1.4 Situation in Armenia	12
1.5 Rationale for the current study	12
2. Methods	13
2.1 Study Design	13
2.2 Study Setting	13
2.3 Study Participants	14
2.4 Sample Size Calculation	14
2.5 Data Collection	15
2.6 Study Instrument	16
2.7 Study Variables	17
2.8 Statistical Analysis	18
2.9 Ethical Considerations	19
3. Results	19
3.1 Response Rate	19
3.2 Descriptive Statistics	20
3.3 Simple Logistic Regression Analysis	22
3.4 Multiple Logistic Regression Analysis	22
4. Discussion	23
4.1 Main Findings	23
4.2 Strengths of The Study	25
4.3 Study Limitations	26

5. Recommendations.....	27
References.....	28
Tables.....	34
Table 1-a. Family sociodemographic characteristics.....	34
Table 1-b. Child’s health	35
Table 1-c. Pregnancy related factors	35
Table 1-d. Parental and family characteristics.....	37
Table 1-e. Family environmental exposures	38
Characteristics.....	38
Table 2.1 Simple logistic regression analysis between the cancer status and its potential risk factors	40
Table 2.2 Simple logistic regression analysis between child’s exposure to second-hand smoke and factors potentially related to childhood cancer.....	41
Table 2.3 Association between cancer status and child’s second hand smoke exposure controlled for the confounder.....	41
Table 3. Multiple logistic regression model of determinants of childhood cancer in Armenia (n=229).....	41
Figures.....	42
Figure 1. Childhood cancer incident cases during 2008-2018 years among less than 18 years old children in Armenia.....	42
Figure 2. Flow chart outlining the study sample selection.....	43
Figure 3. Three-year childhood cancer incidence per 100 000 population aged 0-14 years ...	44
Figure 4. Receiver operating characteristic curve of the final predictive model of determinants of childhood cancer in Armenia	45
Appendices	46
Appendix 1. Medical Record Review Form.....	46
Appendix 2. Journal Form	47
Appendix 3. Informed Consent Form.....	48
Appendix 4. Questionnaire for Telephone Interview with Mothers.....	54

List of Abbreviations

ALL	Acute lymphoblastic leukemic
AUC	Area under curve
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
DALY	Disability adjusted life-years
DNA	Deoxyribonucleic acid
HC	Hematology Center
HIV	The human immunodeficiency virus
IARC	The International Agency for Research on Cancer
IRB	Institutional review board
LMIC	Low/middle income country
OR	Odds ratio
PCBDCA	Pediatric Cancer and Blood Disorders Center of Armenia
PNET	Primitive neuroectodermal tumor
ROC	Receiver operating characteristic
SD	Standard deviation
SEER	The Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
SPSS	Statistical Package for the Social Sciences
TNF alfa	Tumor necrosis factor-alfa
WHO	World Health Organization

Acknowledgement

Foremost, I would like to express my deepest appreciation to my primary advisor Dr. Anahit Demirchyan for her invaluable contribution, immense knowledge, and persistent support. She was my source of encouragement and inspiration during this study. My sincere gratitude to my secondary advisor Dr. Lusine Abrahamyan for her guidance, professional contribution and constructive critique during the thesis preparation process.

I wish to extend my special thanks to Dr. Varduhi Petrosyan, Dean of Gerald and PatriciaTurpanjian School of Public Health, and Dr. Vahe Khachadourian for their professionalism, continuous support and guidance. I am thankful to the MPH faculty and CHSR team for their readiness to help during the study.

I would like to thank the administration and staff of Hematology Center after Prof. Yeolyan and Pediatric Cancer and Blood Disorders Center of Armenia for giving their permission and providing support and understanding throughout the process of my work.

This project would not be achievable without the help of my friends. Thanks to all of my friends who helped me during the hardest time of data collection, especially Anahit Vardanyan, Arevik Chalyan, Maria Badikyan, Martin Harutyunyan, Nare Martirosyan, and Yeva Margaryan for their devotion. I am very grateful to all my MPH friends, especially Tatev Arakelyan, Meri Sahakyan, Kristina Sargsyan, and Rohith Sharan for their unfailing support and encouragement throughout the study.

I would like to acknowledge the support and trust of my parents, who continuously encouraged me to achieve my goals. Finally, I am thankful to all the people whose support was a milestone in the realization of this project.

Abstract

Background: Childhood cancer is a leading cause of death among children aged 0-19 years worldwide. Each year, 300,000 new cases of childhood cancer are diagnosed around the world. Given the differences between pediatric cancer incidence rates, types, and trends in different countries, it is important to conduct studies to find country-specific risk factors of this disease. To our knowledge, so far, no studies were conducted exploring factors associated with childhood cancer in Armenia.

Aim: The aim of this study was to identify possible risk factors for childhood cancer in Armenia.

Methods: The study used a case-control study design. The study setting was the only specialized pediatric hematology and oncology center in Armenia, located at the Hematology Center in Yerevan. The cases were patients of this center aged 14 years or younger, diagnosed with malignant disease. The controls were patients of the same center, but diagnosed with non-malignant disease. Data were collected from the hospital registry and followed with telephone interviews with mothers of the participants. The study instrument was developed and pretested prior to the data collection. The main domains of the questionnaire were: family sociodemographic characteristics, parental demographics, child health, pregnancy-related factors, and family environmental exposures. The analysis included descriptive, then simple and multiple logistic regression analyses to fit a model of risk factors of childhood cancer among the study population.

Results: Overall, 234 participants (117 cases, 117 controls) were included in the study. The study identified that maternal usage of folic acid during pregnancy was protective against childhood cancer. Children born with these mothers had almost two times lower odds of developing cancer (OR=0.54; 95% CI: 0.31-0.94). On the contrary, experiencing horrifying/terrifying event(s) during pregnancy (OR=2.19; 95% CI: 1.18-4.07) and having induced abortions before getting pregnant with the given child (OR=2.94; 95% CI: 1.45-5.96) were associated with two-three-fold higher odds for a child to develop cancer.

Conclusion: This study identified three important modifiable risk factors for childhood cancer in Armenia, all related to the period of pregnancy. These findings are consistent with the literature and indicate the need for improved pregnancy care, including education of reproductive age women and their family members on the importance of stress reduction during pregnancy, avoidance of induced abortions via practicing safe birth control methods and using folic acid prior to conception and during pregnancy.

1. Introduction

1.1 Background: Childhood or pediatric cancer is a very rare condition among children. Still, it is the major cause of death among children 0-19 years old worldwide.¹ Each year, approximately 300,000 new cases of pediatric cancer are diagnosed around the world.^{2,3} The most common three types of pediatric cancers are leukemias, brain tumors, and lymphomas. Leukemia is a malignant transformation of bone marrow and blood, and is the most common type of cancer, constituting approximately 28-30% of all pediatric cancers.^{4,5} The second most common cancers are central nervous system tumors, constituting up to 26% of all pediatric cancers. Lymphomas are in the third place; these cancers start and develop in lymph system but can involve the bone marrow or other organs during the progression.^{4,5}

1.2 Disease burden: Childhood cancer incidence rates vary between 50-200 per million worldwide; these represent 0.5-4.6% of all cancers according to the World Health Organization (WHO).⁶ The data collected from registries worldwide during 2001-2010 years show incidence rates of cancer in children aged 0-19 years to constitute 155.8 per million person-years.³ The latest reviews showed that pediatric cancer rates have slightly increased during the last decades. At the same time, the disease became more controlled, and the survival has been improved; the survival rate is roughly 80% at 5 years, compared with a 58% survival rate in the 1970s.^{7,8} According to the report of the Surveillance, Epidemiology, and End Results (SEER) Program, on 1st January, 2015, there were 269,336 (estimated prevalence) children and young adults (0.34% of the 0-19 years old population) in the United States who had ever been diagnosed with malignant disease.⁹ Global estimate for the number of new childhood cancer cases is projected to increase from 12.7 million in 2008 to up to 22.2 million in 2030.¹⁰

There are considerable differences in pediatric cancer incidence rates, cancer types, and clinical features between high-income countries and low/middle-income countries (LMICs).

Most probably, these differences are attributable to the different environmental, behavioral, genetic, and hygienic factors and early or delayed exposures to infections in these countries.^{2,11} These differences dictate the necessity of country-specific investigation of factors related to the incidence of pediatric cancer.¹² The incidence rates are underestimated in LMICs because of underdiagnosis, the lack of population-based cancer registries, and registration. Approximately 80% of newly diagnosed patients with pediatric cancer live in LMICs. However, one should consider that more than 30% of the population in those countries are children.¹³ Pediatric cancer incidence demonstrates higher increasing trends in LMICs compared with high-income countries.³ Estimation of the burden of pediatric cancer in disability-adjusted life-years (DALYs) showed that approximately 80% of DALYs lost from cancer are in LMICs, at the same time more than 75%¹⁴ of the world population lives there, and for cancer care, they have only approximately 5% of the global resources.¹¹ The cure rates of pediatric cancer differ as well, in high-income countries the cure rate is approximately 80%, but in some LMICs, it is only 20%.¹⁵

1.3 Risk Factors

1.3.1 Demographic factors

The risk factors that may cause or contribute to the occurrence of childhood cancer conditionally could be divided into demographic (age, sex, ethnicity), environmental/extrinsic, intrinsic (birth weight, maternal age, etc.) and genetic factors.^{16,17} In terms of age, the highest rates of childhood cancer are reported among infants and 15-19-year-old individuals.¹⁸ The prevalence of childhood cancer among males is slightly higher. For neuroblastomas and germ cell tumors, the male/female ratio ranges between 1.04 and 1.64. However, some cancer types (e.g., Wilms tumor) are more common among girls.¹⁹ There are differences in childhood cancer risk between different races.¹⁹ The incidence of most types of cancer is relatively higher among whites compared with blacks or Hispanics. On the other

hand, Hispanic children have a slightly higher incidence rate for acute lymphoblastic leukemia (ALL) than white children. Some types of cancer are completely absent in some races (e.g. Ewing sarcoma among blacks). These differences could be explained by both genetic and environmental factors and by the interactions between these factors.¹⁹

1.3.2 Environmental factors

Environmental or extrinsic factors influence the child's body from outside. For example, there is a well-established, supportive data confirming that ionizing radiation and prior chemotherapy contribute to pediatric cancers.^{16,17,19} Chemotherapies conducted by alkylated agents and topoisomerase inhibitors for treating leukemias, lymphomas, or sarcomas have been elucidated as causal factors for the development of secondary cancers among children. These chemotherapeutic agents cause direct DNA damage in both malignant and normal cells of the host at the same time.^{20,21} The potential maternal risk factors should be divided into exposures prior to pregnancy, during pregnancy, and child's exposure after birth. A number of meta-analyses and case-control studies were conducted to find associations between diverse exposures and pediatric cancer; the results are conflicting, which might be because of inherent weaknesses and biases of the conducted studies (recall bias and selection bias). Because of these limitations, finding a causal relationship between possible risk factors and childhood cancer is quite difficult.¹⁶

Nevertheless, some studies show a strong association between pesticide exposure and acute lymphoblastic leukemia (ALL),²² weak associations between coffee consumption during pregnancy and ALL,²³ as well as perinatally performed X-ray, parental marijuana and cocaine usage and childhood rhabdomyosarcoma. Maternal usage of marijuana has been found to be associated with 11 times higher risk of having a child with acute myeloblastic leukemia (AML).²⁴ The previous history of miscarriages dramatically increases the risk for ALL^{24,25,26} and induced abortions - for neuroblastoma.²⁷ A meta-analysis has identified

protective effects of perigestational maternal folic acid supplementation,²⁸ day care in infancy²⁹ and breastfeeding^{30,31} for ALL, as well as vegetable, fruit and multivitamin usage during the first trimester of pregnancy for primitive neuroectodermal tumors (PNET) in the offspring.^{24,32} Maternal antenatal stress was suggested to be associated with certain malignancies among the offspring.³³ According to a population-based case-control study, parental occupation (agricultural worker, electrician, driver, mechanic) could be associated with increased risk of childhood brain tumors.³⁴ Other environmental risk factors include maternal and paternal smoking^{35,36} and alcohol usage,³⁷ which are associated with slightly increased risk for ALL and neuroblastoma.

The International Agency for Research on Cancer (IARC) has classified agents into four groups: Group 1-Carcinogenic to human (120 agents, e.g., alcoholic beverages, Epstein-Barr virus, Haematite mining, Hepatitis B virus, tobacco smoke, second-hand smoke exposure, wood dust, tamoxifen and so on), Group 2A-Probably carcinogenic to humans (83 agents, e.g., lead compounds (inorganic), malaria, non-arsenical insecticides, petroleum refining, red meat. etc.), Group 2B-Possibly carcinogenic to humans (314 agents, magnetic fields (extremely low-frequency), printing processes, pickled vegetables. etc.), Group 3-Not classifiable as to its carcinogenicity to human (500 agents, e.g., paint manufacture, rock (stone) wool, slag wool, acetaminophen, phenol and so on).^{38,39}

Several chronic infections (HIV, Epstein-Barr) have a causal effect on oncogenesis.⁴⁰ These and other infections, which increase the chances of childhood cancer have major relevance in LMICs.^{2,19}

1.3.3 Intrinsic factors

Inherent factors that are not influenced by outside are intrinsic factors. Several studies found linear associations with high birth weight and leukemia, primary brain tumor, soft tissue sarcoma and neuroblastoma.^{16,19,41-44} The reasons behind the relation between birth

weight and pediatric cancer are not fully investigated, but there are several hypothesis, such as the role of insulin-like growth hormone,⁴¹ fetal and maternal genetic factors,¹⁷ and more cells under the risk to become malignant.⁴⁵ The risk of hepatoblastoma is inversely correlated with very low birth weight.^{16,46,47} Advanced parental age increases the risks for several health-related problems, including cancer. A large pooled analysis found that older maternal age has a positive linear relationship with the most common types of childhood cancers (leukemia, lymphoma, brain tumors, Wilms tumor, and sarcomas) and with each 5 years of maternal age increase, the risks are increased by 6-15%.⁴⁸ The risk for ALL was demonstrated to be greater among children of older parents.⁴⁸⁻⁵⁰

1.3.4 Genetic factors

The direct causes for childhood cancer are not fully identified yet, and the majority of the identified risk factors influence on genes, causing de novo mutations, which have their unique, determined place on cancer pathogenesis.¹⁶ The role of different known risk factors (environmental, genetic) in oncogenesis is approximately 5-10% among children, and a huge part of contributing factors are still unknown.¹⁹ Hereditary basis has been identified for only up to 5% of pediatric cancers. Approximately 37% of retinoblastomas and 7% of Wilms' tumors are hereditary.⁵¹ There are several syndromes which are predisposing to childhood cancer, e.g., Ataxia-telangiectasia to ALL and lymphoma,⁵² Down syndrome to ALL (20-fold increased risk),⁵³ Fanconi anemia to AML,⁵⁴ Li-Fraumeni syndrome to soft tissue sarcomas,⁵⁵ and WAGR syndrome to Wilms' tumors.⁵⁶

Linnet et al.⁵⁷ suggested a classification of pediatric cancer risk factors. They separated above mentioned risk factors into three categories: known, suggestive, and limited. Known factors include genetic/congenital disorders (familial neoplastic syndromes, various genetic syndromes, chromosomal alterations)⁵⁸, age, ethnics, gender, and several environmental factors such as irradiation, prior chemotherapy, and infections. Suggestive factors include a

family history of cancer, reproductive factors (maternal age, prior miscarriage, preterm birth), and some other environmental factors (residential pesticides, alcohol, cured meats, or the protective effects by fruits and vegetables)⁵⁹. Limited factors include some environmental factors: influences of war, disasters, child care, magnetic fields, paternal smoking, parental occupational exposure).

Given the described uncertainty, further large-scale studies are required to explain potential genome-environment interactions that cause pediatric cancers.

1.4 Situation in Armenia

According to the report of the National Institute of Health in Armenia, there were 684 total cases of newly diagnosed childhood cancers between 2008-2018 among patients less than 18 years old (Figure 1). According to the data of January 1, 2018, there were 35 children newly diagnosed with cancer (in 2017) out of 595,800 children aged 0-14 living in the Republic of Armenia (17 boys and 18 girls), and the number of those children living with cancer was 178. At the same time, 19 out of 165,200 adolescents aged 15-19 were newly diagnosed with malignant neoplasms (16 boys and 3 girls).

After the establishment of the Pediatric Cancer and Blood Disorders Center of Armenia (PCBDCA) in the Hematology Center (HC) after Prof. Yeolyan in February 2019, the majority of pediatric cancer patients in Armenia get their treatment there, as this is the only center which provides comprehensive diagnostic, treatment and follow-up services for children with oncological and hematological malignancies.⁶⁰

1.5 Rationale for the current study

As the cancer rates are increasing worldwide ^{61,62} and the reasons for increasing incidence rates are still not fully discovered, research is required to further explore the factors affecting childhood cancer development.^{2,19} Discovering the possible risk factors of pediatric cancer is imperative for making progress in the development of preventative strategies. Given

the differences between pediatric cancer incidence rates, types and trends in different countries, it is important to conduct studies to find country-specific risk factors of this disease. To our knowledge, so far, no studies were conducted exploring factors associated with childhood cancer in Armenia.

1.6 Aim of the study and research questions

The aim of this study was to identify possible risk factors for childhood cancer in Armenia.

The research questions were the following:

- What are the potential demographic, environmental, or intrinsic risk factors associated with childhood cancer in Armenia? (primary)
- Is there an association between passive smoking in children and childhood cancer in Armenia? (secondary)

2. Methods

2.1 Study Design

A case-control study was utilized to address the research questions. This design is convenient for comparing multiple exposures and rare diseases within a short-time period. Furthermore, this research method is relatively inexpensive and quick. Finally, the design gives the opportunity to examine multiple potential risk factors at the same time.

2.2 Study Setting

The study was conducted in the HC, Yerevan, Armenia. The rationale for choosing HC is that it is the only specialized hospital in Armenia, which provides comprehensive diagnostic and curative services for patients with blood system diseases, and the only center in Armenia where children with solid and hematologic malignancies get comprehensive care is located there.⁶³

2.3 Study Participants

The target population for the study was children diagnosed with cancer in Armenia. The study population was patients aged 14 and less years, who was recently diagnosed with pediatric cancer and/or received treatment at the PCBDC A.

Cases included patients aged 14 years and less, diagnosed with a malignant disease at the PCBDC A in 2017-2020, permanently living in Armenia, and alive during the time of the survey.

Controls were patients aged 14 years and less, diagnosed with a not malignant disease at the PCBDC A during the years 2017-2020, and permanently living in Armenia.

Mothers were chosen as key informants, and the rationale for choosing them was mainly explained by the need to gather information about exposures to potential risk factors before and during pregnancy and delivery, as the mothers are better aware of that.

Exclusion criteria were the absence of contact information with patient's mother or her inability to speak in Armenian.

2.4 Sample Size Calculation

The formula for the sample size to test the difference in proportions was used for sample size calculation. The sample size was calculated with the level of significance of 0.05 and the power of 80%. According to a large-scale case-control study conducted in Northern California, the proportion of children exposed to cigarette smoke both prenatally and after birth due to parental smoking was 15% among cases with ALL and 9% among controls.⁶⁴ We took these proportions and the detectable effect difference of 12%, which gave a total sample size of 230 or 115 in each group.

$$n = \frac{(Z_{\frac{\alpha}{2}} \sqrt{2pq} + Z_{\beta} \sqrt{p_1q_1 + p_2q_2})^2}{\Delta^2}$$

Power=80%, $Z_{\beta}=0.84$ (standard normal variate for power),

$\alpha=0.05$, $Z_{\alpha/2}=1.96$ (standard normal variate for level of significance),

\bar{p} =average proportion of exposed, measure of variability

\bar{q} = average proportion of unexposed

$p_1 - p_2$ =effect size or different in proportions expected

$P_{case\ exp} = 15\%$ (based on literature)

$P_{control\ exp} = 9\%$

Effect difference=12%

$$n = \frac{(Z_{\alpha/2} \sqrt{2\bar{p}\bar{q}} + Z\beta \sqrt{p_1q_1 + p_2q_2})^2}{\Delta^2} = \frac{(1.96\sqrt{2*0.12*0.88} + 0.84\sqrt{0.15*0.85 + 0.09*0.91})^2}{0.12^2} = \frac{(0.9 + 0.3844)^2}{0.14^2} = \frac{1.65}{0.12^2}$$

=115 (in each group)

Therefore, $n=230$ (115 cases, 115 controls)

2.5 Data Collection

The student investigator conducted the extraction of sample of recently diagnosed patients from the hospital's registry database, after getting permission from the HC's administration.

All children aged 14 years or less with malignant (cases) or benign (controls) diseases, who, based on the PCBDC's database, were diagnosed or got a care in the PCBDC during 2017-2020, formed the sampling frame of the study.

The student investigator gathered cases from the hospital's registry. Cases meeting the eligibility criteria were selected. Due to the limited number of cases, a census of children meeting the inclusion criteria for cases was conducted. Overall, 189 cases were identified.

Controls were selected from the same HC as the cases, among those children who utilized inpatient or outpatient services of the center within the selected period for other than

cancer conditions. Overall, 212 eligible controls were selected, which was a census of eligible controls for the period of October 2017 through March 2020.

For both cases and controls, the information about child's ID, age, diagnosis and the year of diagnosis (clinical data) was extracted in the Medical Record Review Form (Appendix 1) and the identifiable data and contact information was recorded separately in the Journal form (Appendix 2). The latter was also used to calculate the response rate. All the contacted participants were presented with the oral consent form (Appendix 3). All the phone interviews were carried out by trained interviewers, after assuring the eligibility of the child.

In case of any missing data in the medical record/chart, the information was filled during the telephone interview.

The telephone interviews were conducted with the mothers of eligible cases and controls. Three attempts were made to contact each mother. The student-investigator and six trained interviewers worked in parallel and completed the data collection during the period of 17-29 of March, 2020.

2.6 Study Instrument

The study questionnaire (Appendix 4) was developed based on literature review and similar studies conducted in other countries and adapted based on local specificities.^{9,17,46,66,67} The structured questionnaire included 62 items combined in 5 main domains of potential risk factors:

1. Family sociodemographic characteristics, which included residency (marzes), residential status (city, village or other, living borderline), family size, general standards of living, and average monthly spending of the family.
2. Parental demographics: age, education, and occupation of parents, family status (nuclear, extended, divorced), smoking and drinking habits of the family, child exposure to

second-hand smoke, child relative with cancer (siblings, parents, grandparents, and siblings of parents), and the blood ties among parents or grandparents.

3. Child health: birth weight, birth anomalies, birth order, childhood infections, chronic diseases, X-ray exposure.

4. Pregnancy characteristics: mode of delivery (vaginal delivery, caesarian section), BMI before getting pregnant, breastfeeding, consumption of folic acid, caffeine consumption, alcohol usage, exposure to ultrasound or X-ray, any illness and any antibiotic usage during pregnancy, use of contraceptive, history of miscarriages or abortions, information about mother's trauma-induced stress, smoking, and second-hand smoke exposure.

5. Environmental factors: the source of water (tap, bottled, filtered, well water), the presence of backyard/garden and the use of any pesticides/herbicides there, the year the house was constructed (a proxy for asbestos exposure), the mode of house heating, residential proximity to the chemical industry and mining.

The questionnaire was pre-tested among three mothers of 0-14 years old children before its utilization in the actual study. Based on the feedback from these interviews, appropriate changes were made in the questionnaire.

2.7 Study Variables

The dependent variable (outcome) in this study was the presence or absence of malignancy in a child aged 0-14 years based on the confirmed diagnosis in the medical records.

Independent variables were potential risk factors of childhood cancer, including child's demographic characteristics (age, sex, residency, diagnosis), family sociodemographic characteristics (residential status, family size, general living standards and income), parental characteristics (age, education, employment, marital status, alcohol usage, smoking status, relatives with cancer), child's health (birth weight, birth order, birth defects, any acute

infection during infancy, any chronic diseases, X-ray exposure), pregnancy related factors (gestation age and mode of the delivery, BMI before getting pregnant, breastfeeding, folic acid usage, coffee drinking, alcohol usage, any illness, antibiotics usage, number of X-ray and ultrasound examinations during the pregnancy, oral contraceptives, miscarriages, abortions before the pregnancy, horrifying/terrifying events during the pregnancy, smoking and second hand smoke exposure during pregnancy) and family environmental exposures (the source of drinking water, pesticide usage, the year the house was constructed, the mode of house heating, chemical industry or mining dump within 10km of the house).

2.8 Statistical Analysis

The data entry and analysis were performed using IBM SPSS 23 and Stata/SE 13.0 software. Single data entry with subsequent cleaning and logic and range checking was used.

The characteristics of cases and controls were summarized using descriptive statistics. For categorical variables, counts and percentages were calculated; means and standard deviations were used to describe continuous variables. For comparing continuous variables between cases and controls, the t-test and for categorical variables, the Chi-square test was used. Simple, then multiple logistic regression analyses were conducted between the risk factors and the outcome of cancer status to determine the direction and strength of the detected associations while controlling for the other independent variables. All the variables with p values less than 0.25 during univariate analysis and all the available potential risk factors of childhood cancer known from the literature were further tested in the multivariable analysis to find independent risk factors of childhood cancer among the selected sample. Subsequently, all the variables that lost their significance after controlling for other variables in the model were excluded. The model fit was tested using the Hosmer – Lemeshow goodness of fit test (calibration) and the area under the receiver operating characteristic (ROC) curve (discrimination). Additionally, the association between child's second-hand

smoking and cancer status was examined in multivariable logistic regression analysis after controlling for the identified confounders (variables significantly associated with both cancer status and second-hand smoke exposure in the univariate analyses).

2.9 Ethical Considerations

The AUA Institutional Review Board within the School of Public Health at the American University of Armenia reviewed and approved the study protocol. Permission was obtained from the HC's and PCBDC's head managers in order to conduct data extraction. Oral consent form (Appendix 3) was used to explain the study participants the aim of the study, their rights to refuse or quit the participation whenever they want as well as to assure them about their anonymous participation and data confidentiality. The paper journal forms (Appendix 2) that included all the identifiable information of participants were kept separate from the questionnaires, and medical record review forms to avoid disclosure and were destroyed after finishing the data checking and cleaning. All participants were provided with AUA CHSR telephone numbers in case of study-related concerns or other questions.

3. Results

3.1 Response Rate

We planned to include 115 participants in each group. Based on the list of potentially eligible patients from the Hematology Center after prof. Yeolyan, a total of 189 eligible patients were identified for cases, and 212 eligible patients for controls (Figure 2). However, we could not contact 68 subjects from cases and 78 from controls due to various reasons (incorrect phone number, mother was not available at the time of data collection, no response, being out of the country or non-existing telephone number). Out of 121 contacted cases, completed interviews were obtained from 117 mothers, and four mothers refused to participate. Of the 134 contacted controls, interviews were conducted with 117 mothers, and

17 mothers refused to participate. Hence, the refusal rate was 3.3% among cases and 12.7% among controls. Overall, the response rate was 61.9% for the cases and 55.2% for the controls. With this sample size, the study power for identifying a 12% difference in proportions of independent variables between cases and controls was 0.80.

3.2 Descriptive Statistics

The following frequency of conditions was observed among the study sample. Of the cases, 42.7% (n=50) were diagnosed with acute lymphoblastic leukemia, 16.2% (n=19) with lymphoma, 9.4% (n=11) with different types of sarcoma, 7.7% (n=9) with central nervous system (CNS) and Wilms tumors, 2.6% (n=3) with germ cell tumor, 1.7% (n=2) with histiocytosis and aplastic anemia, and per one case (0.9% each) with hepatoblastoma and retinoblastoma. Of the controls, 32.5% (n=38) were diagnosed with thrombocytopenia, 20.5% (n=24) with hemolytic anemia, 18.8% (n=22) with other anemia (B12 or iron deficiency or combined), 9.4% (n=11) with hemorrhagic vasculitis, 5.1% (n=6) with lymphadenopathy, 4.3% (n=5) with coagulopathy, 3.4% (n=4) with hemophilia, 1.7% (n=2) with splenomegaly, and per one child (0.85% each) with atopic dermatitis, leukemoid reaction, leukopenia, spherocytosis and thromboembolism of pulmonary artery.

The descriptive statistics on family sociodemographic characteristics, parental demographics, child health, pregnancy-related factors and family environmental exposures for the total sample and separately for the cases and controls are presented in Tables 1a-e.

The geographical distribution of cases and controls was significantly different in the Artsakh Republic and marginally different in Gegharkunik marz. From both areas, there were more cases than controls.

A higher proportion of cases than controls were living borderline (Table 1-a). The mean age of children was 7.1 (SD 3.79) years for the cases and 5.3 (SD 3.52) years for the controls.

There were more males than females in both groups: about 57.3% (n=67) of cases and 62.4% (n=73) of controls were males (Table 1-b).

A statistically significant difference was detected between cases and control regarding their mother's taking folic acid during pregnancy, with a lower proportion of mothers of cases than controls taking it (38.3% versus 53.4%, $p < 0.01$, Table 1-c). Compared with mothers of controls, a significantly higher proportion of mothers of cases had induced abortions before getting pregnant with the given child. Also, compared to mothers of controls, a significantly higher proportion of mothers of cases reported experiencing a highly stressful event(s) during the pregnancy. Exposure to X-ray during the pregnancy was very low in both groups (none of the mothers of cases and six of the mothers of controls), but still significantly higher among mothers of controls (Table 1-c). There were a number of marginally significant differences ($0.05 \leq p < 0.1$) between cases and controls, including a higher proportion of cases having a family member diagnosed with cancer and mother using alcohol-containing drinks (Table 1-d). A marginally higher proportion of cases than controls reported child's presence during pesticide/herbicide sprays and child's eating fruits without washing under running water, while a marginally higher proportion of controls reported living within 10 km from mining dumps (Table 1-e). Other variables were not different between cases and controls.

Based on the data of HC (which includes all the diagnosed CC cases in the center from March 2017 through March 2020, regardless of their survival status), we calculated three year incidence rate of cancer per 100 000 0-14 years old population for each marz. The latter is presented in Figure 3, which demonstrates the highest childhood cancer incidence rate in Vayots Dzor marz (42.1), followed by Artsakh republic (31.6) and Tavush marz (32.5).

3.3 Simple Logistic Regression Analysis

Table 2 presents the results of simple logistic regression analysis to assess crude associations between childhood cancer and each independent variable. The estimated crude OR of the association between the folic acid intake before/during pregnancy and having a child with cancer was 0.54 (95% CI: 0.32-0.91), showing folic acid having a protective effect. Experiencing horrifying/terrifying events during the pregnancy was associated with higher odds of having a child with cancer with a crude OR of 2.46 (95% CI: 1.37-4.44). Having any induced abortion before getting pregnant with the given child (OR=3.19 95% CI: 1.6-6.35) was significantly associated with the child's cancer status. Conversely, the number of induced abortions before getting pregnant with the given child was associated with lower odds of having a child with cancer (OR=0.70; 95% CI: 0.43-0.56).

3.4 Multiple Logistic Regression Analysis

The next step in the analysis was looking at the association between cancer status and child's second-hand smoke exposure controlled for confounders. There was no statistically significant association detected among cancer status and child's second-hand smoke exposure (OR=1.41 95% CI: 0.84-2.36; p=0.19) during univariate analysis. Furthermore, the confounder analysis showed that there were no variables significantly associated with both cancer status and second-hand smoking. As folic acid usage during pregnancy was significantly associated with child's cancer status and marginally significantly with child's second-hand smoke exposure, this variable was included in the multivariable analysis between cancer status and second-hand smoke exposure as a possible confounder of that association (Table 2.2). Nevertheless, the results did not indicate a significant relationship between cancer status and second-hand smoke exposure after adjusting for this confounder.

As the final step, a logistic regression model was fitted with the outcome of childhood cancer status to identify the independent risk factors of cancer (Table 3). The p-value of the

Hosmer-Lemeshow goodness-of-fit test of the final model was 0.615, indicating a good fit (acceptable level of calibration) and AUC ROC=0.699 (Figure 4). The final model contained the following set of independent determinants of childhood cancer status: folic acid usage during pregnancy (OR=0.54; 95% CI: 0.31-0.94; p=0.030), having induced abortions before getting pregnant (OR=2.94; 95% CI: 1.45-5.96; p=0.003), experiencing horrifying/terrifying events during the pregnancy (OR=2.19; 95% CI: 1.18-4.07; p=0.013) and having a family member diagnosed with cancer (OR=1.71; 95% CI: 0.93-3.18; p=0.085).

According to these, mother's taking folic acid during pregnancy was associated with 46% lower odds of having a child with cancer compared to not taking folic acid during pregnancy. The history of induced abortions before getting pregnant with the given child was associated with 2.94 times higher odds for the child to develop cancer. Also, the odds of developing cancer among those children with mothers who experienced horrifying/terrifying event during the pregnancy was 2.19 (95% CI: 1.18-4.07) times the odds of developing cancer among those children with mothers reporting no history of horrifying/terrifying event during the pregnancy.

4. Discussion

4.1 Main Findings

As there was no data about childhood cancer risk factors investigated in the country, the current study aimed to reveal independent risk factors of childhood cancer among children aged 0-14 years old in Armenia and identify whether there was an association between child's exposure to second-hand smoke and childhood cancer in Armenia.

Our finding on the protective effect of maternal folic acid usage before and during pregnancy on the risk of development of childhood cancer is consistent with the literature, as many studies found that taking folic acid before and during pregnancy was significantly

inversely associated with the cancer risk (leukemia, brain tumor) in a child.^{28,59,68–70,71} And, several studies from the United States and Canada recorded a decrease of childhood cancer incidence (neuroblastoma, Wilms tumor, and PNETs) after folic acid fortification.^{72–74} The folate is considered as an essential nutrient for the cell multiplication (as a coenzyme for DNA synthesis) and cell homeostasis (metabolism and regeneration).⁷⁵ According to WHO standards for maternal and neonatal care, mothers should start taking 400 µg folic acid daily two months before getting pregnant and take until 12 weeks of pregnancy.⁷⁶

According to our study findings, the history of induced abortions before pregnancy increases the risk of childhood cancer threefold. There are studies indicating that the past history of induced abortions is associated with cancer in children (leukemia, neuroblastoma, soft tissue sarcoma) without specifying the number of abortions.^{27,77–79} However, some studies report a lack of such association or not significant associations.^{80–82} A research conducted by Children's Cancer Group and the Pediatric Oncology Group identified two times higher risk of neuroblastoma in a child, whose mother has a history of two or more previous induced abortions.²⁷

This study confirmed that the history of maternal trauma-induced stress during pregnancy is a risk factor for developing childhood cancer in the offspring. This finding was consistent with a population-based cohort study conducted in Denmark and Sweden about stressful events during pregnancy and increased risks of childhood cancer development. This cohort study included 39,002 children; whose mothers had psychological stress (parental death) during pregnancy. The study detected an increased risk for the offspring for leukemia (standardized incidence ratio (SIR), 1.49; P=0.004), testicular cancer (SIR, 1.80; P=0.02) and colon cancer (SIR, 3.95; P=0.003) before the age of 15 years.⁸³ There are several other studies, both clinical³³ and preclinical,⁸⁴ indicating the role of the stress during pregnancy and increased risk for childhood cancer. There is a proposed hypothesis of a model of interaction

between stress and carcinogenesis. Stress is associated with the growing production of cytokines (interleukin 1,6 (IL-1,6) and tumor necrosis factor-alfa (TNF alfa)), as well as reduction of the natural killer cell activity and down regulation of its activator. The mechanism behind the carcinogenesis is considered to be the mediated inhibition of the enzyme, which initiates activation of the cancerous cells to get under immune surveillance, and after the inhibition of the enzyme the newly generated malignant cells would continue growing without being checked by the immune system.⁸⁴

Above mentioned mechanisms could underlay the findings of a cohort study conducted in Israel, which observed higher cancer incidence (for leukemia, lymphoma, and melanoma) among bereaved Jewish people.⁸⁵ In addition, there was anecdotal information from physicians about the increase of childhood cancer rates among the earthquake survivors in the earthquake area in Armenia.

This study failed to identify significant associations between child's second hand-smoking and childhood cancer or other well-known environmental exposures confirmed as risk factors for childhood cancer, such as pesticides, chemicals, radiation, or others. The underlying reason for missing these associations could be the small size of the studied sample.

4.2 Strengths of The Study

To our knowledge, this is the first study conducted to investigate risk factors of childhood cancer in Armenia among 0-14 years old population.

Both cases and controls have been identified from the same data sources, which helps to reduce the selection bias as the participants were coming from the same base population with equal chances of having the exposure.

Both cases and controls were selected from the same hospital, which is the only place in the county where patients with hematologic and oncologic diseases can get specialized

diagnosis and treatment. This means that patients represent the entire country and contributes to the reduction of the selection bias, leading to more generalizable results.

To minimize the recall bias, participants were selected, giving preference to the recently diagnosed patients.

4.3 Study Limitations

The telephone interviews were conducted by six trained interviewers; they were aware of the participant's case and control status, and the interviewer bias was a threat, which could lead to inconsistency.

The other potential limitation of the current study could be recall bias due to the long interval between the onset of the child's disease and the interview. Also, cases might remember events, which participants in the control group might disregard. Additionally, social desirability bias was a potential threat to the study.

Patients with missing contact information could differ from the participants with the contact information available, and it is not clear how that difference, if existing, could alter the study findings.

Twenty-three patients diagnosed with cancer in the HC during the same period (2017-2020) who did not survive by the time of the study were excluded from the survey because of ethical considerations of conducting interviews with their mothers. This could have influenced the study findings if the non-survivors were different from the study cases. However, the analysis of the available characteristics of the non-survivors demonstrated that they did not differ from the survivors in terms of age, sex, residency, and the cancer type (except lymphoma, which was much less diagnosed among the non-survivors).

The inclusion of participants with different types of cancer as cases is another limitation of this study, as there are cancer-specific risk factors, which cannot be identified with this approach.

5. Recommendations

According to our findings, children with mothers who did not take folic acid during pregnancy were at higher risk of developing childhood cancer, thus, preventative interventions should focus on the education of future mothers on this issue. Folic acid supplementation before and during pregnancy is currently recommended by WHO and the MoH of Armenia to prevent birth defects of the brain and spine (neural tube defects). Based on our study findings, it is protective against childhood cancer as well. Therefore, all women should be advised by primary care physicians and/or gynecologists to consume the recommended dosage of folic acid before conception and during pregnancy. In addition, there is a need to increase awareness among women about the importance of using safe and effective methods of birth control and family planning to avoid induced abortions. Education of reproductive age women and their family members on the importance of stress reduction during pregnancy is another important area for improvement.

Further larger-scale studies are recommended to conduct to find other potential risk factors of childhood cancer that this study could not reveal given its limited power. Also, it would be worthwhile to conduct studies among patients with the same type of childhood cancer in order to detect childhood cancer-specific risk factors.

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Tables

Table 1-a. Family sociodemographic characteristics

Characteristics	Cases n = 117	Controls n = 117	Total n = 234
Marz distribution, %(n)			
Yerevan	29.1 (34)	38.5 (45)	33.8 (79)
Aragatsotn	6.0 (7)	2.6 (3)	4.3 (10)
Ararat	6.0 (7)	9.4 (11)	7.7 (18)
Armavir	9.4 (11)	11.1 (13)	10.3 (24)
Gegharkunik*	9.4 (11)	3.4 (4)	6.4 (15)
Kotayk	7.7 (9)	10.3 (12)	9.0 (21)
Lori	6.0 (7)	6.0 (7)	6.0 (14)
Shirak	6.8 (8)	6.8 (8)	6.8 (16)
Syunik	2.6 (3)	5.1 (6)	3.8 (9)
Tavush	4.3 (5)	4.3 (5)	4.3 (10)
Vayots Dzor	3.4 (4)	1.7 (2)	2.6 (6)
Artsakh**	7.7 (9)	0.9 (1)	4.3 (10)
Javakhq	1.7 (2)	0.0 (0)	0.9 (2)
Place of residence, %(n)			
City	65.8 (77)	67.5 (79)	66.7 (156)
Village	34.2 (40)	32.5 (38)	33.3 (78)
Family size, mean (SD)	5.3 (1.62)	5.2 (1.57)	5.3 (2.4)
Living in a border city/village, %(n) *	12.8 (15)	6.8 (8)	9.8 (23)
Living standards, %(n)			
Below average	22.5 (25)	23.3 (27)	22.9 (52)
Average	61.3 (68)	62.3 (72)	61.7 (140)
Above average	16.2 (18)	14.7 (17)	15.4 (35)
Family spending, %(n)			
Less than 100 000 drams	20.9 (23)	21.6 (25)	21.2 (48)
From 100 001-300 000 drams	44.5 (49)	39.7 (46)	42.0 (95)
Above 300 000 drams	3.6 (4)	9.5 (11)	6.6 (15)
Refused to answer	30.9 (34)	29.3 (34)	30.1 (68)

*Marginal significance (p-value between 0.05 and 0.1)

**p-value <0.05

***p-value <0.01

Table 1-b. Child's health

Characteristics	Cases n =117	Controls n =117	Total n =234
Child's age (during the interview) (years), mean (SD)	7.1 (3.79)	5.3 (3.52)	6.2 (3.66)
Sex, %(n)			
Male	57.3 (67)	62.4 (73)	59.8 (140)
Female	42.7 (50)	37.6 (44)	40.2 (94)
Birth weight (grams), %(n)			
Less than 2500	7.7 (9)	12.8 (15)	10.3 (24)
From 2500 to 4000	88.0 (103)	82.9 (97)	85.5 (200)
More than 4000	3.4 (4)	3.4 (4)	3.4 (8)
Don't remember	0.9 (1)	0.9 (1)	0.9 (2)
Birth order, mean (SD)	1.8 (0.86)	1.8 (1.03)	1.8 (0.95)
Birth defect, %(n)	4.3 (5)	3.4 (4)	3.8 (9)
Any infections during the first year of child's life (number), mean (SD)	0.7 (1.12)	0.9 (1.31)	0.8 (1.22)
Chronic disease, %(n)	7.7 (9)	8.5 (10)	8.1 (19)
X-ray before disease diagnosis, %(n)	31.6 (37)	37.6 (44)	34.6 (81)
Number of X-rays before disease diagnosis, mean (SD)	2.0 (1.34)	1.9 (2.09)	1.9 (1.72)

*Marginal significance (p-value between 0.05 and 0.1)

**p-value <0.05

***p-value <0.01

Table 1-c. Pregnancy related factors

Characteristics	Cases n =117	Controls n =117	Total n =234
Delivery mode, %(n)			
Vaginal	74.1 (86)	71.6 (83)	72.8 (169)
C-section	25.9 (30)	28.4 (33)	27.2 (63)
Term of delivery (months), mean (SD)	8.9 (0.32)	8.7 (0.79)	8.8 (0.56)
Mother's BMI before pregnancy, mean (SD)	22.6 (3.94)	22.5 (3.81)	22.5 (3.88)
Breastfeeding, %(n)	93.9 (108)	90.5 (105)	92.2 (213)
Breastfeeding duration (months), mean (SD)	14.0 (8.59)	14.2 (8.31)	14.1 (8.45)
Folic acid during pregnancy, %(n)**	38.3 (44)	53.4 (62)	45.9 (106)
Coffee drinking during pregnancy, %(n)			
Yes, daily	68.7 (79)	58.6 (68)	63.6 (147)
Yes, not daily	12.2 (37)	19.8 (23)	16.0 (37)
No	20.3 (47)	21.6 (25)	20.3 (47)

Characteristics	Cases n =117	Controls n =117	Total n =234
Coffee consumption during pregnancy (cups/day), mean (SD)	2.1 (0.91)	2.0 (0.89)	2.0 (0.9)
Alcohol usage during pregnancy, %(n)			
Yes	0.0 (0)	0.0 (0)	0.0 (0)
Yes, less than weekly	7.8 (9)	5.2 (6)	6.5 (15)
No	92.2 (106)	94.8 (110)	93.5 (216)
Ultrasound number during pregnancy, mean (SD)	4.7 (2.33)	5.3 (2.93)	5.0 (2.63)
X-ray exposure during pregnancy, %(n)**	0.0 (0)	5.2 (6)	2.6 (6)
Trimester, %(n)			
First		16.7 (1)	
Second		83.3 (5)	
Third		0.0 (0)	
Antibiotic usage during pregnancy, %(n)	10.4 (12)	6.9 (8)	8.7 (20)
Illness during pregnancy, %(n)	40.0 (46)	35.7 (41)	37.8 (87)
Oral contraceptive usage, %(n)	3.5 (4)	4.3 (5)	3.9 (9)
Miscarriages before getting pregnant, %(n)	21.9 (25)	21.7 (25)	21.8 (50)
Number of miscarriages, mean (SD)	1.5 (0.71)	1.54 (1.33)	1.52 (1.02)
Induced abortions before getting pregnant, %(n) ***	30.7 (35)	12.2 (14)	21.4 (49)
Number of induced abortions before getting pregnant, mean (SD) *	1.8 (1.58)	3.2 (2.46)	2.1 (2.02)
Horrifying/terrifying events during the pregnancy, %(n)***	37.6 (44)	19.7 (23)	28.6 (67)
Second hand smoke exposure during pregnancy, %(n)			
Daily	25.2 (29)	20.9 (24)	23.0 (53)
Less than daily	40.0 (46)	35.7 (41)	37.8 (87)
Never	34.8 (40)	43.5 (50)	39.1 (90)

*Marginal significance (p-value between 0.05 and 0.1)

**p-value <0.05

***p-value <0.01

Table 1-d. Parental and family characteristics

Characteristics	Cases n =117	Controls n =117	Total n =234
MOTHER			
Mother's age at the time of the interview (years), mean (SD)	33.91 (4.89)	33.24 (5.97)	33.57 (5.43)
Mothers education, %(n)			
Elementary or secondary school	33.6 (39)	27.4 (32)	30.5 (71)
Professional technical education	28.4 (33)	35.0 (41)	31.8 (74)
Institute/University or post-graduate	37.9 (44)	37.6 (44)	37.8 (88)
Chemical exposure within 24 months before getting pregnant, %(n)	1.7 (2)	5.1 (6)	3.4 (8)
Marital status, %(n)			
Married	93.2 (109)	96.6 (113)	94.9 (222)
Widowed	1.7 (2)	0.0 (0)	0.9 (2)
Divorced/separated	5.1 (6)	3.4 (4)	4.3 (10)
Ever cigarette smoking, %(n)	2.6 (3)	5.1 (6)	3.8 (9)
Current cigarette smoking, %(n)	0.0 (0)	0.9 (1)	0.45 (1)
Alcohol usage, %(n)*			
Never	47.0 (55)	56.0 (65)	51.5 (120)
Less than 1 drink in a month	44.4 (52)	35.3 (41)	39.9 (93)
1-3 drinks in a month	8.5 (10)	5.2 (6)	6.9 (16)
1-3 drink in a week	0.0 (0)	3.4 (4)	1.7 (4)
FATHER			
Father's age (years), mean (SD)	38.6 (6.23)	37.8 (7.85)	38.2 (7.04)
Father's education, %(n)			
Elementary or secondary school	47.9 (56)	41.0 (48)	44.4 (104)
Professional technical education	20.5 (24)	19.7 (23)	20.1 (47)
Institute/University or post-graduate	31.6 (37)	39.3 (46)	35.5 (83)
Father's occupation during 24 months prior the wife's pregnancy, %(n)			
Agricultural worker	20.5 (24)	15.4 (18)	17.9 (42)
Electrician	3.4 (4)	5.1 (6)	4.3 (10)
Driver	12.0 (14)	14.5 (17)	13.2 (31)
Mechanic	5.1 (6)	1.7 (2)	3.4 (8)
Other	59.0 (69)	63.2 (74)	61.1 (143)
Father's ever smoking, %(n)	83.6 (97)	76.7 (89)	80.2 (186)
Father's currently smoking, %(n)			
Yes, daily	62.8 (75)	67.5 (79)	65.5 (154)
Yes, less than daily	6.8 (8)	2.6 (3)	9.4 (11)
No	16.2 (19)	14.5 (17)	30.8 (36)
Fathers daily smoked cigarette number (unit), mean (SD)	21.9 (9.82)	20.9 (9.49)	21.4 (9.66)

Table 1-d. Parental and family characteristics

Characteristics	Cases n =117	Controls n =117	Total n =234
MOTHER			
FAMILY CHARACTERISTICS			
Second hand smoke exposure of the child before getting the disease, %(n)			
Daily	21.4 (25)	17.9 (21)	19.7 (46)
Less than daily	33.3 (39)	28.2 (33)	30.8 (72)
Never	45.3 (53)	53.8 (63)	49.6 (116)
Smokers in the households, mean (SD)	1.0 (0.76)	0.9 (0.72)	1.0 (0.74)
Binge drinking in family, %(n)			
Yes	6.8 (8)	6.0 (7)	6.4 (15)
No	86.3 (101)	90.6 (106)	88.5 (207)
Don't know/not sure	6.8 (8)	3.4 (4)	5.1 (12)
Core family member with diagnosed cancer, %(n)*	34.2 (40)	23.1 (27)	28.6 (67)
Blood ties among parents, %(n)	3.4 (4)	2.6 (3)	3.0 (7)
Blood ties among grandparents, %(n)*	0.9 (1)	4.3 (5)	2.6 (6)

*Marginal significance (p-value between 0.05 and 0.1)

**p-value <0.05

***p-value <0.01

Table 1-e. Family environmental exposures

Characteristics	Cases n =117	Controls n =117	Total n =234
Drinking water, %(n)			
Municipal/tap water	85.3 (99)	85.2 (98)	85.3 (197)
Wells water	9.5 (11)	6.1 (7)	7.8 (18)
Bottled water	2.6 (3)	2.6 (3)	2.6 (6)
Filtered water	2.6 (3)	6.1 (7)	4.3 (10)
Pesticide usage, %(n)	21.6 (25)	18.4 (21)	20.0 (46)
Frequency of pesticide spray during a year, mean (SD)	3.8 (3.93)	3.4 (2.54)	3.6 (3.24)
Pesticide/herbicide sprayer, %(n)			
The mother	2.6 (3)	1.7 (2)	4.3 (5)
The father	7.7 (9)	9.4 (11)	17.1 (20)
Another worker	11.1 (13)	5.9 (7)	17.1 (20)
Child's presence during sprays, %(n)*			
Often	0.0 (0)	0.9 (1)	0.43 (1)
Sometimes	5.12 (6)	0.9 (1)	2.9 (7)
Never	16.2 (19)	15.4 (18)	15.8 (37)

Table 1-e. Family environmental exposures

Characteristics	Cases n =117	Controls n =117	Total n =234
Fruit washing under running water before giving to the child, %(n)*	96.2 (25)	80.0 (16)	89.1 (41)
The average age of the house (years), mean (SD)	35.9 (16.07)	32.8 (18.15)	34.4 (17.11)
House heating mode, %(n)			
Hot water (e.g., Baxi)	33.6 (38)	38.9 (44)	36.3 (82)
Electric heater	9.7 (11)	10.6 (12)	10.2 (23)
Chimney stove, which burns gas, oil, or kerosene	16.8 (19)	15.0 (17)	15.9 (36)
Wood or coal stove	34.5 (39)	33.6 (38)	34.1 (77)
Dung cake stove	5.3 (6)	1.8 (2)	3.5 (8)
Housing conditions, %(n)			
Good	32.5 (38)	26.1 (30)	29.3 (68)
Average (meets basic needs)	61.5 (72)	67.8 (78)	64.7 (150)
Poor	6.0 (7)	6.1 (7)	6.0 (14)
Chemical industries within 10km from the house, %(n)	13.7 (16)	12.2 (14)	12.9 (30)
Mining dump within 10km from the house, %(n)*	7.7 (9)	14.8 (17)	11.2 (26)

*Marginal significance (p-value between 0.05 and 0.1)

**p-value <0.05

***p-value <0.01

Table 2.1 Simple logistic regression analysis between the cancer status and its potential risk factors

Characteristics	OR	95% CI	P-value
Yerevan residents	0.65	0.38-1.13	0.129
Gegharkunik residents	2.93	0.91-9.49	0.073
Artsakh residents	9.67	1.20-77.57	0.033
Living borderline	2.00	0.82-4.92	0.130
Family member with diagnosed cancer	1.73	0.97-3.08	0.061
Father's agricultural work	1.42	0.72-2.78	0.308
Mother's usage of alcohol			
Never*	1.00		
Less than a drink in a month	1.52	0.88-2.62	0.130
1-3 drinks in a month or week	1.20	0.47-3.09	0.706
No exposure to second-hand smoke during pregnancy	0.69	0.41-1.18	0.177
Folic acid usage during pregnancy	0.54	0.32-0.91	0.021
Having any induced abortions before getting pregnant	3.19	1.60-6.35	0.001
Mean number of abortions before pregnancy	0.70	0.50-0.98	0.042
Horrifying/terrifying events during the pregnancy	2.46	1.37-4.44	0.002
X-ray exposure during pregnancy	0.49	0.43-0.56	0.999
Blood ties among child's grandmother-grandfathers	0.19	0.02-1.69	0.138
Second-hand smoke exposure to a child	1.41	0.84-2.36	0.192
Fruit washing under running water before giving to the child	1.72	0.86-3.41	0.124
Mining dump within 10 km from the house	0.48	0.21-1.13	0.092

*Reference group.

Table 2.2 Simple logistic regression analysis between child’s exposure to second-hand smoke and factors potentially related to childhood cancer

Characteristics	OR	95% CI	P-value
Family member with diagnosed cancer	1.11	0.63-1.95	0.726
Having a father doing agricultural work	1.57	0.79-3.08	0.195
Folic acid usage during pregnancy	0.60	0.36-1.01	0.057
Induced abortions before getting pregnant	1.43	0.75-2.70	0.275
Horrifying/terrifying events during pregnancy	1.31	0.74-2.31	0.353
Mean number of induced abortions before pregnancy	1.45	0.93-2.25	0.104

Table 2.3 Association between cancer status and child’s second hand smoke exposure controlled for the confounder

Characteristics	OR	95% CI	P-value
Second-hand smoke exposure	1.25	0.74-2.12	0.390
Folic acid usage during pregnancy	0.55	0.33-0.94	0.028

Table 3. Multiple logistic regression model of determinants of childhood cancer in Armenia (n=229)

Characteristics	aOR	95% CI	P-value
Folic acid usage during pregnancy	0.54	0.31-0.94	0.030
Induced abortions before getting pregnant	2.94	1.45-5.96	0.003
Horrifying/terrifying events during the pregnancy	2.19	1.18-4.07	0.013
Family member diagnosed with cancer	1.71	0.93-3.18	0.085

Model of fit statistics: *Hosmer & Lemeshow goodness of fit test, p=0.615*

ROC AUC=0.699

Figures

Figure 1. Childhood cancer incident cases during 2008-2018 years among less than 18 years old children in Armenia

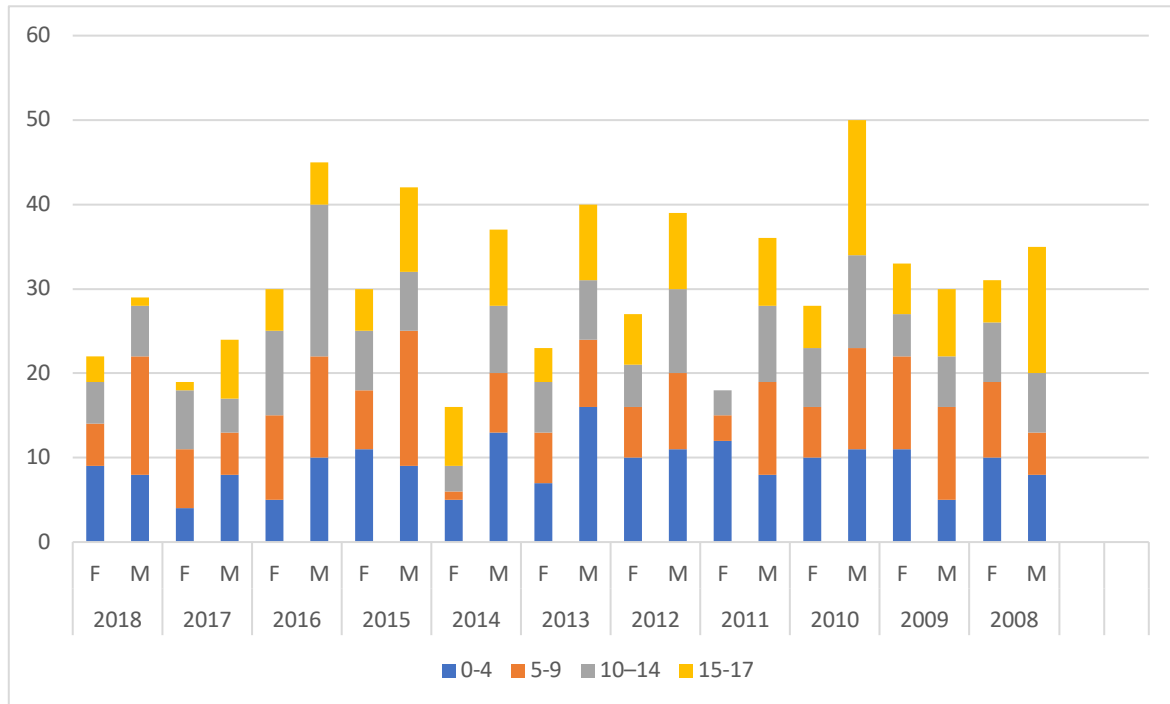


Figure 2. Flow chart outlining the study sample selection

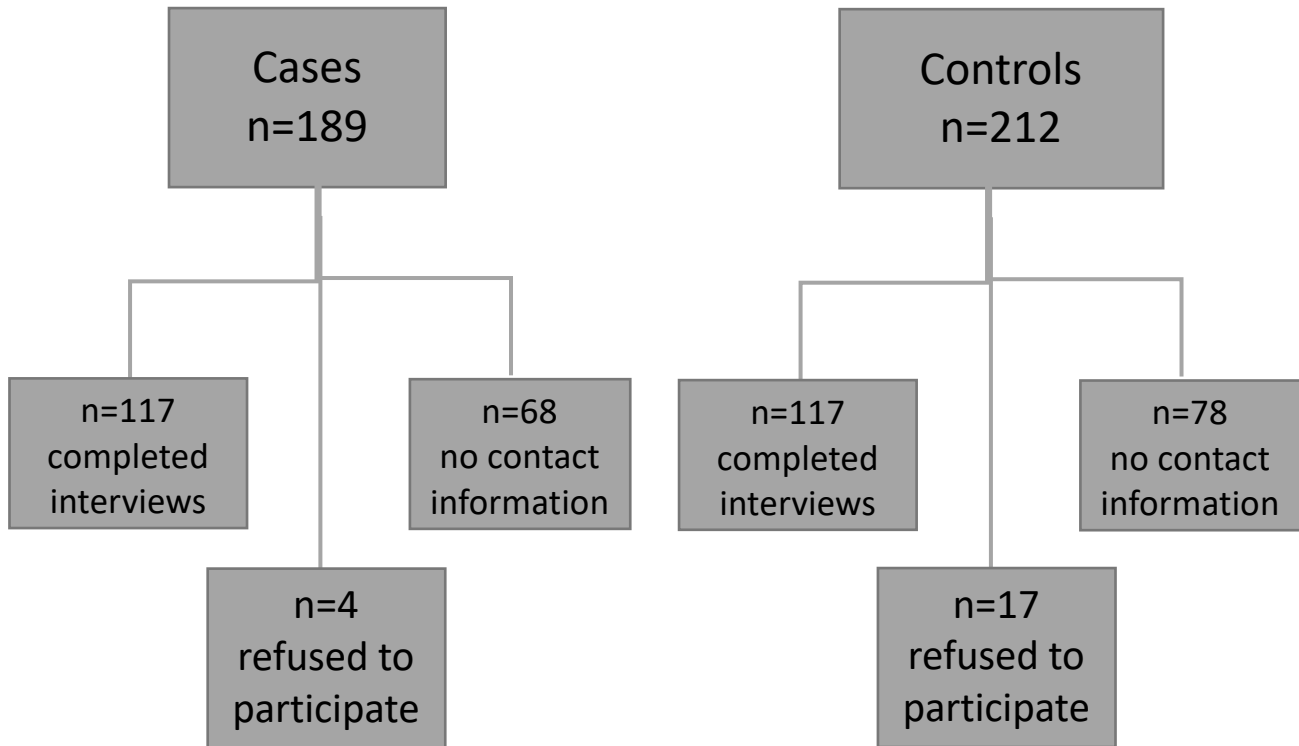


Figure 3. Three-year childhood cancer incidence per 100 000 population aged 0-14 years

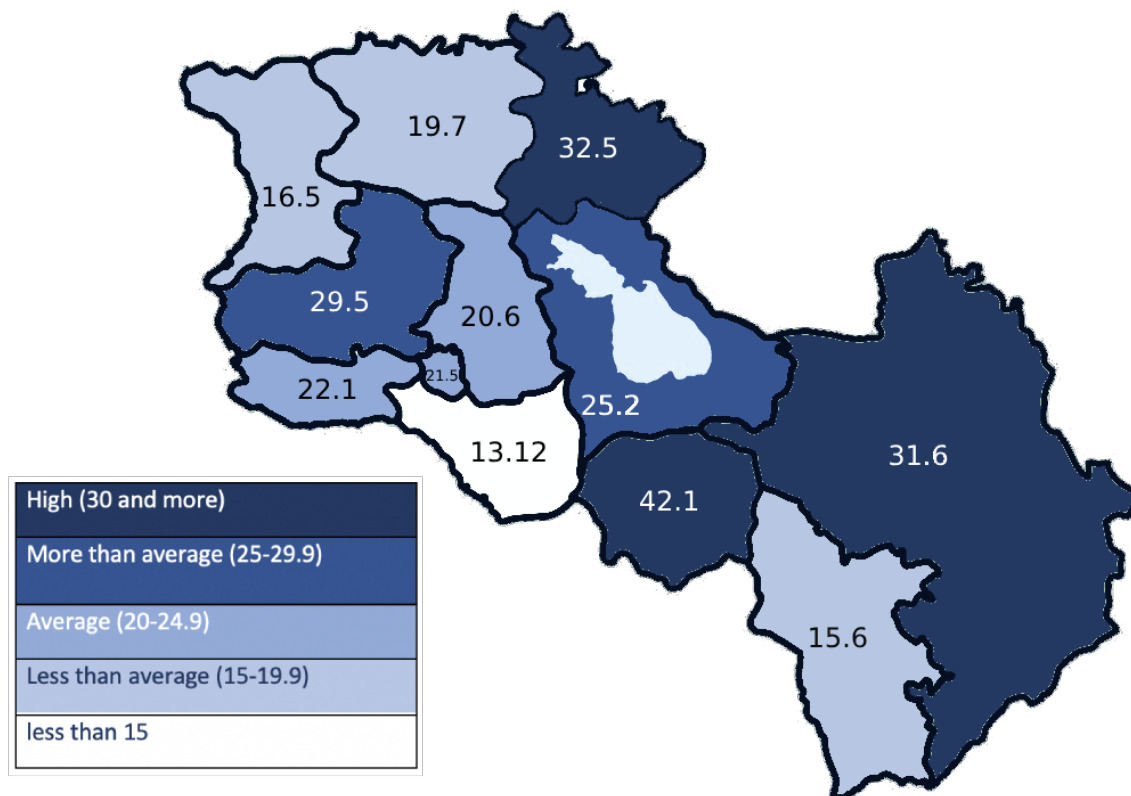
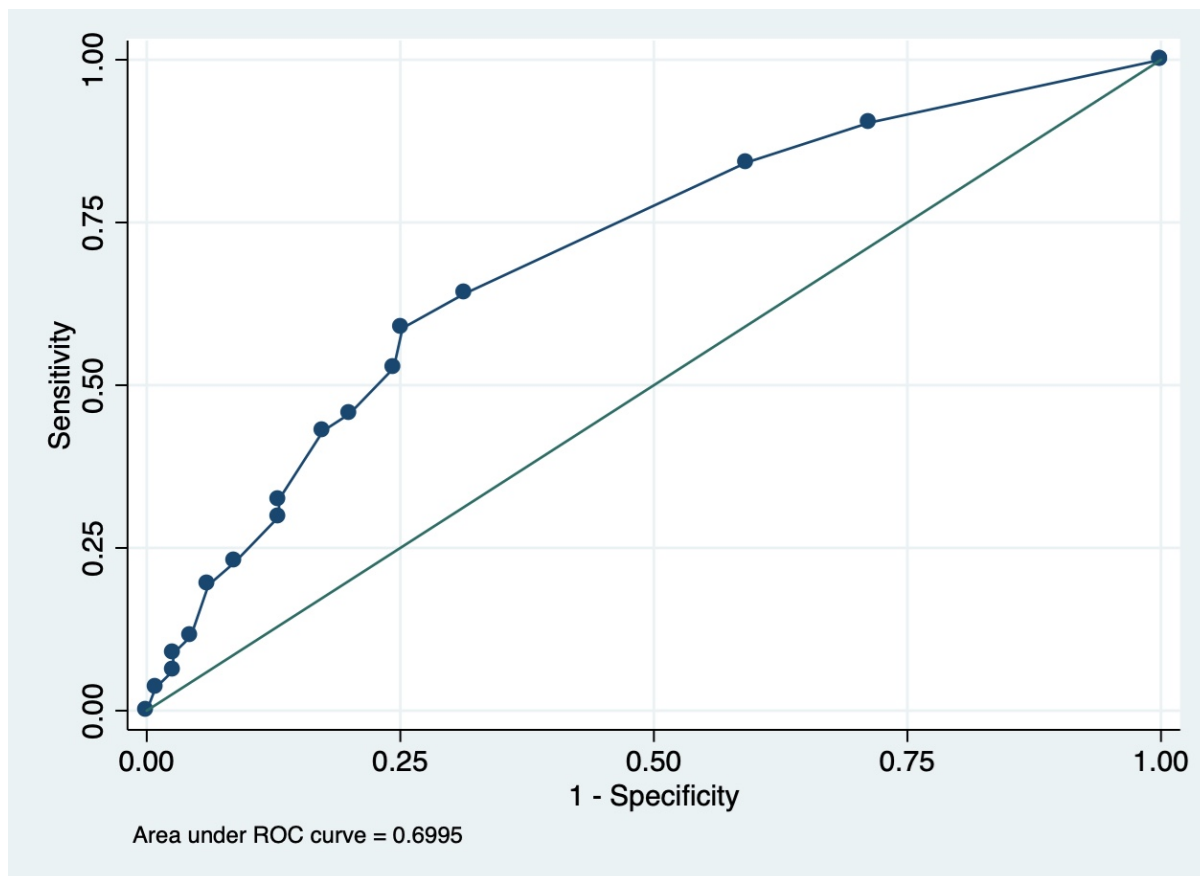


Figure 4. Receiver operating characteristic curve of the final predictive model of determinants of childhood cancer in Armenia



Appendices

Appendix 1. Medical Record Review Form

General Information

ID# ____|____ (Patient ID/Medical card ID)

Date of birth ____/____/____

Patient sex Male____ Female____

Date of admission ____/____/____

Main clinical diagnosis _____

Appendix 3. Informed Consent Form

Իրազեկ համաձայնագիր և մասնակցի սկրինինգային ձև

Բարև Ձեզ: Ես Մանուշակն եմ: Ես մանկական արյունաբանության և ուռուցքաբանության բժիշկ օրդինատոր եմ, նաև՝ Հայաստանի ամերիկյան համալսարանի Հանրային առողջապահության բաժնի ավարտական կուրսի ուսանող: Այժմ, ես աշխատում եմ իմ մագիստրոսական թեզի վրա, որն ուսումնասիրում է Հայաստանում մանկական քաղցկեղի զարգացման ռիսկի գործոնները: Ձեր հեռախոսահամարը տրամադրել է արյունաբանական կենտրոնը: Ունեմ մեկ հարց պարզելու համար, արդյոք կարող եք լինել մեր հետազոտության մասնակից:

(Հարցազրուցավարի համար) Ես Հայաստանի ամերիկյան համալսարանի Առողջապահական ծառայությունների հետազոտման և զարգացման կենտրոնից եմ: Իմ անունն է ____: Այժմ Հանրային առողջապահության բաժնի ավարտական կուրսի ուսանողի թեզի շրջանակներում իրականացվում է մի հետազոտություն, որի նպատակն է Հայաստանում մանկական քաղցկեղի զարգացման ռիսկի գործոնների բացահայտումը: Ես զանգահարում եմ արյունաբանական կենտրոնի կողմից տրամադրած հեռախոսահամարով: Ունեմ մեկ հարց պարզելու համար, արդյոք կարող եք լինել մեր հետազոտության մասնակից, թե ոչ:

Ձեր տանը բնակվում է ____ տարեկան _____ անուն-ազգանունով երեխա, ով վերջին մեկ-երկու տարվա ընթացքում հետազոտվել կամ բուժվել է արյունաբանական կենտրոնում:

Եթե ՈՉ – Շնորհակալություն հայտնել մասնակցին և ավարտել:

Եթե, ԱՅՈ - Ճշտում եք, թե ու՞մ հետ եք խոսում, հետո միայն, եթե պատասխանողը մայրն է՝ ներկայացնում եք իրազեկ համաձայնության պայմանները: Եթե պատասխանողը մայրը չէ ապա ներկայացրեք հետազոտության մանրամասները, և հեռախոսազանգին պատասխանողից խնդրեք երեխայի մոր հեռախոսահամարը:

Հայաստանի ամերիկյան համալսարան
Հանրային առողջապահության ֆակուլտետ
Գիտահետազոտական էթիկայի թիվ 1 հանձնաժողով
Իրազեկ համաձայնության ձև

Վերնագիր-Մանկական քաղցկեղի զարգացման ռիսկի գործոնները Հայաստանում
Հետազոտական թիմ/ղեկավարներ-Անահիտ Դեմիրճյան, Լուսինե Աբրահամյան

Բարև Ձեզ: Ես Մանուշակն եմ, մանկական արյունաբանության և ուռուցքաբանության բժիշկ-օրդինատոր եմ, ես նաև Հայաստանի ամերիկյան համալսարանի Հանրային առողջապահության ֆակուլտետի ավարտական կուրսի ուսանող եմ: Մենք ավարտական աշխատանքի շրջանակներում իրականացնում ենք ուսումնասիրություն, որի նպատակն է բացահայտել Հայաստանում մանկական քաղցկեղի զարգացման ռիսկի գործոնները: Ուսումնասիրությունն իրականացվում է այն 230 մայրերի շրջանում, ում երեխաների տարիքը 14 տարեկան կամ փոքր են, և վերջերս հետազոտվել և/կամ բուժում են ստացել Մանկական քաղցկեղի և արյան հիվանդությունների կենտրոն՝ Արյունաբանական կենտրոնում:

(Հարցազրուցավարի համար) Ես Հայաստանի ամերիկյան համալսարանի Առողջապահական ծառայությունների հետազոտման և զարգացման կենտրոնից եմ: Իմ անունն է: Մենք ավարտական աշխատանքի շրջանակներում իրականացնում ենք մի հետազոտություն, որի նպատակն է Հայաստանում մանկական քաղցկեղի զարգացման ռիսկի գործոնների բացահայտումը: Ուսումնասիրությունն իրականացվում է այն 230 մայրերի շրջանում, ում երեխաների տարիքը 14 տարեկան կամ փոքր են, և վերջերս հետազոտվել և/կամ բուժում են ստացել Մանկական քաղցկեղի և արյան հիվանդությունների կենտրոն՝ Արյունաբանական կենտրոնում:

Դուք հրավիրված եք մասնակցել այս հետազոտությանը, քանի որ վերջերս Ձեր երեխան ախտորոշվել և/կամ բուժում է ստացել Մանկական քաղցկեղի և արյան հիվանդությունների կենտրոն՝ Արյունաբանական կենտրոնում, որտեղից և Ձեր կոնտակտային տվյալները վերցվել են: Ձեր մասնակցությունը այս հարցմանը սահմանափակվում է միայն այս հեռախոսային հարցազրույցով, որը կտևի 15-20 րոպե: Ես կխնդրեի Ձեզ մասնակցել այս հետազոտությանը և կիսվել Ձեր փորձառությամբ՝ երեխայի հիվանդանալուն նախորդող ժամանակահատվածի վերաբերյալ: Հարցերը հիմնականում վերաբերվում են հղիության ընթացքում, դրանից առաջ և հետո որոշ գործոնների, որոնց ենթարկվել եք Դուք (մայրը) և ձեր երեխան:

Ձեր մասնակցությունն այս հետազոտությանը կամավոր է: Ձեզ ոչինչ չի սպառնում, եթե Դուք հրաժարվեք մասնակցել այս հետազոտությանը: Դուք կարող եք հրաժարվել պատասխանել ցանկացած հարցի կամ ցանկացած պահի ընդհատել հարցազրույցը: Ձեր մասնակցությունը այս հետազոտությանը որևէ վտանգ չի ներկայացնում Ձեզ համար, և չմասնակցելու կամ ցանկացած պահի ընդհատելու պարագայում չի ազդի Արյունաբանական կենտրոնում ձեր ներկայիս կամ ապագա բուժման վրա: Ձեր կողմից տրամադրված տվյալները կարևոր են հետազոտության համար: Այս հարցազրույցին Ձեր մասնակցությունը չի ենթադրում որևէ ուղղակի շահ Ձեզ համար, բայց Ձեր մասնակցությունը կարող է օգնել ավելի լավ հասկանալ այն գործոնները, որոնց հսկողությունը կարող է նպաստել երեխաների առողջության պահպանմանը:

Ձեր կողմից տրամադրված տվյալները, ինչպես նաև բժշկական տվյալները գաղտնի են պահվելու և օգտագործվելու են միայն այս հետազոտության նպատակով: Ձեր անունը, հասցեն կամ հեռախոսահամարը չեն նշվելու հարցաթերթիկի վրա կամ հետազոտության որևէ զեկույցի մեջ և ձեռքբերված բոլոր տվյալները պահվելու են գաղտնի: Ձեր կոնտակտային տվյալները կոչնչացվեն տվյալների հավաքագրումից անմիջապես հետո:

Եթե Դուք ունեք հետագա հարցեր տվյալ հետազոտության մասին, կարող եք կապվել անմիջապես հետազոտության ղեկավար՝ Անահիտ Դեմիրճյանին (+374 60) 612562 հեռախոսահամարով: Եթե Դուք կարծում եք, որ հետազոտության ընթացքում Ձեզ հետ լավ չեն վերաբերվել և/կամ հետազոտությունը Ձեզ վնաս է հասցրել, կարող եք զանգահարել ՀԱՀ-ի Էթիկայի հանձնաժողովի համակարգող՝ Վարդուհի Հայրումյանին, հետևյալ հեռախոսահամարով (010) 6125 61:

Համաձայն եք մասնակցել:

Շնորհակալություն:

Interviewers introduction to the participant

Hello. I am Manushak and I am pediatric hematology/oncology resident-doctor and a graduate student of the Master of Public Health program at the American University of Armenia. Currently, I am working on my master thesis and it is dedicated to the investigation of risk factors of pediatric cancer in Armenia. Your telephone number was provided by Hematology Center. I have a question to clarify whether you can be a participant to our study, or not.

(For the interviewer) I am from the American University of Armenia's Health Services Research and Development Center. My name is _____. In the scope of master thesis project, a research is being carried out, which aims to assess risk factors of pediatric cancer in Armenia. Your telephone number was provided by Hematology Center. I have a question to clarify whether you can be a participant to our study, or not.

Does anyone live in your house with _____ age and _____ name, who recently diagnosed or received treatment in the Hematology Center.

- If NO – thank and finish
- If YES – Ask whether the interviewer is mother or not then go to the consent form. If the phone number belongs to the person other than the mother, present the study, and ask the contact number of the patient's mother from the phone call responder.

American University of Armenia
Turpanjian School of Public Health
Institutional Review Board #1
Consent form

Title-Risk factors of childhood cancer in Armenia

Research team/Advisors-Anahit Demirchyan, Lusine Abrahamyan

Hello. My name is Manushak, I am pediatric hematology/oncology resident doctor and I am a graduate student of the Master of Public Health program at the American University of Armenia. In the scope of master thesis project, a research is being carried out, which aims to assess risk factors of pediatric cancer in Armenia. The research is conducted among 230 mothers, whose children are 14 and less, and were recently diagnosed and/or received treatment at the Pediatric Cancer and Blood Disorders Center of Armenia (PCBDCA) in the Hematology Center (HC) after Prof. Yeolyan.

(Fort the interviewer) I am from the American University of Armenia's Health Services Research and Development Center. My name is _____. In the scope of master thesis project, a research is being carried out, which aims to assess risk factors of pediatric cancer in Armenia. The research is conducted among 230 mothers, whose children are 14 and less, and were recently diagnosed and/or received treatment at the Pediatric Cancer and Blood Disorders Center of Armenia (PCBDCA) in the Hematology Center (HC) after Prof. Yeolyan.

You are invited to participate in this study, as your child diagnosed and get treatment at the Pediatric Cancer and Blood Disorders Center of Armenia (PCBDCA) in the Hematology Center (HC) after Prof. Yeolyan, from where your contact information was extracted. Your participation in this study will involve only the current telephone interview that will last 15-20 minutes. I would like to ask you to participate in this study to share some additional details about the experience before the child getting the disease. The questions are mainly about the possible risk factors, which you and your child have been exposed before or after the child birth.

Your participation in this study is voluntary. There is no penalty if you refuse to participate in this study. You can skip any questions you do not want to answer or even stop the interview. Your participation in the study poses no risk for you and not participating or withdrawing from the study at any time will not affect your current or future treatment at the Hematology center. The information received from you is important for the study. There is no direct benefit from the participation in this study, but your participation will contribute to better understanding the risk factors of pediatric cancer and the control of that factors could lead to prevention of child health.

The information provided by you and the data obtained from the medical records/charts are fully confidential and will be used only for the study. Your name, contact information and other identifiable information will not appear on the questionnaire and final report. Your contact information will be destroyed upon the completion of data collection.

If you have any questions regarding this study you can contact the Principal Investigator of this study, Research Assistant Professor of the Gerald and Patricia Turpanjian School of Public Health, Dr. Anahit Demirchyan at 060 61 2562. If you think you have been hurt by participating in the study or feel you have not been treated fairly you can contact the American University of Armenia Human Protections Administrator, Varduhi Hayrumyan at (060) 61 25 61.

Do you agree to participate?

Thank you.

Appendix 4. Questionnaire for Telephone Interview with Mothers

Questionnaire: Risk factors of Pediatric Cancer in Armenia		
Interviewer ID _____ Interview date ____/____/____ (yyyy/mm/dd) Interview start time __: __ (hh:mm) 24-hour format		
1. Family sociodemographic		
1.	In what marz of Armenia do you live?	1. <input type="checkbox"/> Yerevan 2. <input type="checkbox"/> Aragatsotn 3. <input type="checkbox"/> Ararat 4. <input type="checkbox"/> Armavir 5. <input type="checkbox"/> Gegharkunik 6. <input type="checkbox"/> Kotayk 7. <input type="checkbox"/> Lori 8. <input type="checkbox"/> Shirak 9. <input type="checkbox"/> Syunik 10. <input type="checkbox"/> Tavush 11. <input type="checkbox"/> Vayots Dzor 12. <input type="checkbox"/> Artsakh
2.	What is your residential status?	1. <input type="checkbox"/> City 2. <input type="checkbox"/> Village
3.	How many people live in your family?	_____ persons
4.	Is your city/village located in a border? (Read the options)	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
5.	How would you rate your family's general standard of living? (Read the options)	1. <input type="checkbox"/> Substantially below average 2. <input type="checkbox"/> Little below average 3. <input type="checkbox"/> Average 4. <input type="checkbox"/> Little above average 5. <input type="checkbox"/> Substantially above average

6.	In average, how much money does your family spend monthly? (Read the options)	1. <input type="checkbox"/> Less than 50.000 drams 2. <input type="checkbox"/> From 50,000 – 100,000 drams 3. <input type="checkbox"/> From 100,001 – 200,000 drams 4. <input type="checkbox"/> From 200,001 – 300,000 drams 5. <input type="checkbox"/> Above 300,000 drams 6. <input type="checkbox"/> Refuse to answer
2. Parental demographics		
2.1 MOTHER		
7.	What is your year of birth?	_____ (yyyy)
8.	What is your completed educational level? (Read the options)	1. <input type="checkbox"/> School (less than 9 years) 2. <input type="checkbox"/> School (10-12 years) 3. <input type="checkbox"/> Professional technical education 4. <input type="checkbox"/> Institute/University 5. <input type="checkbox"/> Post-graduate
9.	Did you work with chemicals, gas, benzene, fumes or other harmful products within 24 months prior to getting pregnant with this child?	1. <input type="checkbox"/> Yes→ 1.1 Name the product _____ 2. <input type="checkbox"/> No
10.	What is your marital status? (Read the options)	1. <input type="checkbox"/> Married 2. <input type="checkbox"/> Single 3. <input type="checkbox"/> Widow/Widowed 4. <input type="checkbox"/> Divorced/Separated
2.1.1 Smoking		
11.	Have you ever smoked cigarettes?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No, => <i>Go to Q15</i>
12.	Do you currently smoke cigarettes?	1. <input type="checkbox"/> Yes, daily 2. <input type="checkbox"/> Yes, less than daily, => <i>Go to Q15</i> 3. <input type="checkbox"/> No, => <i>Go to Q15</i>
13.	How many cigarettes per day do you smoke?	_____ cigarettes

2.1.2 Alcohol usage		
14.	On average, how often do you use alcohol containing drinks (vodka, wine, cognac)? (One portion drink includes 1 glass wine or 1 bottle beer or 1 small glass cognac, liqueur or vodka)	1. <input type="checkbox"/> Never 2. <input type="checkbox"/> Less than 1 drink a week 3. <input type="checkbox"/> 1-3 drinks a week 4. <input type="checkbox"/> 4-6 drinks a week 5. <input type="checkbox"/> 7-13 drinks a week 6. <input type="checkbox"/> 14 drinks or more a week

2.2 FATHER		
15.	What is the child's father's year of birth?	_____ (yyyy)
16.	What is child's father's completed educational level? (Read the options)	1. <input type="checkbox"/> Secondary school (less than 10 years) 2. <input type="checkbox"/> High school completed (10-12 years) 3. <input type="checkbox"/> Professional technical education 4. <input type="checkbox"/> Institute/University 5. <input type="checkbox"/> Post-graduate
17.	Did the child's father do the following work during 24 months prior to your getting pregnant with the child? (Read the options)	1. <input type="checkbox"/> agricultural worker 2. <input type="checkbox"/> electrician 3. <input type="checkbox"/> driver 4. <input type="checkbox"/> mechanic 5. <input type="checkbox"/> Other → specify _____
2.2.1 Smoking		
18.	Has he ever smoked cigarettes?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No => <i>Go to Q22</i>
19.	Does he currently smoke cigarettes?	1. <input type="checkbox"/> Yes, daily 2. <input type="checkbox"/> Yes, less than daily => <i>Go to Q22</i> 3. <input type="checkbox"/> No => <i>Go to Q22</i>
20.	How many cigarettes per day does he smoke?	_____ cigarettes

2.3 Family characteristics		
21.	How many of your household members currently smoke?	_____
22.	How often do people smoke in the same room where your child is present, before the child get sick?	1. <input type="checkbox"/> Daily 2. <input type="checkbox"/> Less than daily 3. <input type="checkbox"/> Never
23.	During your pregnancy or after your child birth, does anyone drink alcohol containing drinks 5 or more times every day (e.g., 5 glasses of wine, or 5 bottles of beer or 5 little glasses of cognac, vodka or liqueur).	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No 3. <input type="checkbox"/> Don't know/Not sure
24.	Does any of your core family members, or any of the child's grandfathers, grandmothers, aunts or uncles ever suffered from cancer?	1. <input type="checkbox"/> Yes → 1.1 Relationship with the child _____ 2. <input type="checkbox"/> No
25.	Do you have blood ties with the child's father?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
26.	Whether any of the child's grandmother-grandfathers have blood ties with each other?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
3. Child health		
27.	What was the birth weight of your child? (g) (Read the options)	1. <input type="checkbox"/> Less than 2500 2. <input type="checkbox"/> From 2500 to 4000 3. <input type="checkbox"/> More than 4000 4. <input type="checkbox"/> Don't remember
28.	What is the order of the child in the family?	_____ -th child
29.	Did your child have any birth defect?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
30.	How many times had your child been diagnosed with any infections during the first year of his/her life: including flue or other viral diseases? <i>(Put 0 if none)</i>	_____ times
31.	Was the child diagnosed with any other chronic disease before getting ill with the current disease?	1. <input type="checkbox"/> Yes => 1.1 if yes, specify what disease _____ 2. <input type="checkbox"/> No
32.	Did the child have any exposure to X-ray before getting ill with the current disease?	1. <input type="checkbox"/> Yes => 1.1 if yes, specify, how many times _____ 2. <input type="checkbox"/> No

4. Pregnancy related factors		
33.	How did you deliver the child? (Read the options)	1. <input type="checkbox"/> Vaginal 2. <input type="checkbox"/> C-section
34.	At what pregnancy month did you deliver the child?	1. _____ (month) 2. <input type="checkbox"/> Don't remember
35.	What was your average weight before getting pregnant with this child?	1. <input type="checkbox"/> _____ kg 2. <input type="checkbox"/> Don't know
36.	What is your average height?	1. <input type="checkbox"/> _____ cm 2. <input type="checkbox"/> Don't know
37.	Did you ever breastfeed your child?	1. <input type="checkbox"/> Yes, => 1.1 If yes, for how long? Specify _____ months _____ weeks 2. <input type="checkbox"/> No
38.	Have you taken folic acid during pregnancy with this child?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
39.	Have you taken coffee during pregnancy? (Read the options)	1. <input type="checkbox"/> Yes, daily => 1.1 How many cups per day? _____ 2. <input type="checkbox"/> Yes, not daily 3. <input type="checkbox"/> No
40.	Were you using alcohol containing drinks during pregnancy with this child? (Read the options)	1. <input type="checkbox"/> Yes, weekly or more often 2. <input type="checkbox"/> Yes, less than weekly 3. <input type="checkbox"/> No
41.	How many times did you undergo ultrasound during pregnancy? (Put 0 if none)	_____ times
42.	Were you exposed to X-ray during pregnancy?	1. <input type="checkbox"/> Yes, => 1.1 How many times? _____ 2. <input type="checkbox"/> No → Go to Q45
43.	Trimester of pregnancy at X-ray exposure: (Mark all that apply)	1. <input type="checkbox"/> First 2. <input type="checkbox"/> Second 3. <input type="checkbox"/> Third
44.	Have you taken antibiotics during pregnancy?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
45.	Have you had any illnesses during pregnancy with this child?	1. <input type="checkbox"/> Yes, → 1.1 Please, specify the disease _____ 2. <input type="checkbox"/> No

46.	Have you used oral contraceptives before getting pregnant with this child?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No		
47.	Did you have miscarriages before getting pregnant with this child?	1. <input type="checkbox"/> Yes, => 1.1 How many times? ____ 2. <input type="checkbox"/> No		
48.	Did you have induced abortions before getting pregnant with this child?	1. <input type="checkbox"/> Yes, => 1.1 How many times? ____ 2. <input type="checkbox"/> No		
49.	Have you experienced any horrifying/terrifying event to you during the pregnancy with this child, such as: <i>(read the options, mark all that apply)</i>	1. <input type="checkbox"/> Natural disaster (earthquake, flood, fire, etc.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. <input type="checkbox"/> Violence toward yourself (e.g., beating, rape, stabbing, gunshot)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
3. <input type="checkbox"/> Life threatening accident (e.g., automobile)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
4. <input type="checkbox"/> Sudden (unexpected) death of a loved one		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
5. <input type="checkbox"/> Participation in war-related events		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
6. <input type="checkbox"/> Other terrifying event → 6.1. Please, specify: _____		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
50.	<i>(Ask only mothers who reported ever smoking)</i> How often did you smoke when pregnant with this child? (Read the options)	1. <input type="checkbox"/> Daily 2. <input type="checkbox"/> Less than daily 3. <input type="checkbox"/> Never		
51.	How often did people smoke in the same room with you when you were pregnant with this child? (Read the options)	1. <input type="checkbox"/> Daily 2. <input type="checkbox"/> Less than daily 3. <input type="checkbox"/> Never		

5. Family environmental exposures		
52.	What is the source of drinking water you use in your house?	1. <input type="checkbox"/> Municipal/tap water 2. <input type="checkbox"/> Wells water 3. <input type="checkbox"/> Bottled water 4. <input type="checkbox"/> Filtered water
53.	Do you have a back yard/garden where you use pesticides?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No => Go to Q58
54.	On average, how many times per year do you spray the garden with pesticides?	_____
55.	Who usually carries the procedures of spraying the garden with pesticide/herbicides?	1. <input type="checkbox"/> The mother (you) 2. <input type="checkbox"/> The father 3. <input type="checkbox"/> Other worker
56.	How often is the child present during these sprays (pesticide usage)?	1. <input type="checkbox"/> Often 2. <input type="checkbox"/> Sometimes 3. <input type="checkbox"/> Never
57.	Do you wash fruits under running water (in general or from your garden) before giving it to the child or the child does it before eating those?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
58.	How many years ago your house was constructed (<i>if don't remember, record an estimate</i>)?	_____ years
59.	What is the mode of heating of your house mainly? (Read the options)	1. <input type="checkbox"/> Hot water (e.g., Baxi) 2. <input type="checkbox"/> Electric heater 3. <input type="checkbox"/> Chimney stove, which burns gas, oil, or kerosene 4. <input type="checkbox"/> Wood or coal stove (with chimney) 5. <input type="checkbox"/> Stove for atar burn 6. <input type="checkbox"/> Oil-fired stove, without chimney, "Fujica" 7. <input type="checkbox"/> Fireplace 8. <input type="checkbox"/> Other, specify _____ 9. <input type="checkbox"/> Not heated

60.	How would you rate your housing conditions? (Read the options)	1. <input type="checkbox"/> Good housing conditions 2. <input type="checkbox"/> Average housing conditions (meets basic needs) 3. <input type="checkbox"/> Poor housing conditions 4. <input type="checkbox"/> Other _____
61.	Are there any chemical industries within 10 km from your house?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
62.	Is there a mining dump within 10 km distance from your house?	1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No
Interview end time__ : __ (hh:mm) 24-hour format		

Thank you!

Հարցաշար. Մանկական քաղցկեղի ռիսկի գործոնները Հայաստանում

Հարցազրուցավարի SՀ _____

Ամսաթիվ ___/___/___ (տարի/ամիս/օր)

Սկսման ժամ __:__(ժամ:րոպե՝ 24-ժամյա ձևաչափով)

1. Ընտանիքի սոցիալ-ժողովրդագրական տվյալներ

1.	Հայաստանի ո՞ր մարզում եք բնակվում:	1. <input type="checkbox"/> Երևան 2. <input type="checkbox"/> Արագածոտն 3. <input type="checkbox"/> Արարատ 4. <input type="checkbox"/> Արմավիր 5. <input type="checkbox"/> Գեղարքունիք 6. <input type="checkbox"/> Կոտայք 7. <input type="checkbox"/> Լոռի 8. <input type="checkbox"/> Շիրակ 9. <input type="checkbox"/> Սյունիք 10. <input type="checkbox"/> Տավուշ 11. <input type="checkbox"/> Վայոց Ձոր 12. <input type="checkbox"/> Արցախ
2.	Նշեք՝ Ձեր բնակավայրը քաղա՞ք է, թե գյուղ:	1. <input type="checkbox"/> Քաղաք 2. <input type="checkbox"/> Գյուղ
3.	Քանի՞ անձից է բաղկացած Ձեր ընտանիքը:	_____ մարդ
4.	Ձեր գյուղը/քաղաքը համարվո՞ւմ է, արդյոք, սահմանային:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
5.	Ընդհանուր առմամբ, ինչպե՞ս կգնահատեիք Ձեր ընտանիքի նյութական վիճակը: <i>(Կարդացեք պատասխանները)</i>	1. <input type="checkbox"/> Միջինից բավականին բարձր 2. <input type="checkbox"/> Միջինից քիչ բարձր 3. <input type="checkbox"/> Միջին 4. <input type="checkbox"/> Միջինից քիչ ցածր 5. <input type="checkbox"/> Միջինից բավականին ցածր
6.	Միջինում ամսական որքա՞ն գումար է ծախսում Ձեր ընտանիքը: <i>(Կարդացեք պատասխանները)</i>	1. <input type="checkbox"/> 50,000 դրամից պակաս 2. <input type="checkbox"/> 50,000 – 100,000 դրամ 3. <input type="checkbox"/> 100,001 – 200,000 դրամ 4. <input type="checkbox"/> 200,001 – 300,000 դրամ 5. <input type="checkbox"/> 300,000 դրամ և ավելի 6. <input type="checkbox"/> Հրաժարվում եմ պատասխանել

2. Ծնողների ժողովրդագրական տվյալներ		
2.1 Մայր		
7.	Խնդրում եմ նշել Ձեր ծննդյան տարեթիվը:	_____ (տարի)
8.	Ի՞նչ կրթություն ունեք: (Կարդացեք պատասխանները)	1. <input type="checkbox"/> Դպրոց (9 տարի կամ պակաս) 2. <input type="checkbox"/> Դպրոց (10-12 տարի) 3. <input type="checkbox"/> Միջին մասնագիտական կրթություն 4. <input type="checkbox"/> Ինստիտուտ/Համալսարան 5. <input type="checkbox"/> Հետդիպլոմային
9.	Այս երեխայով հղիանալուն նախորդող 24 ամիսների ընթացքում Դուք աշխատե՞լ եք արդյոք քիմիական նյութերի, գազերի, բենզինի, ծխի, կամ այլ վտանգավոր նյութերի հետ:	1. <input type="checkbox"/> Այո → 1.1 Նշեք, ինչ նյութի հետ _____ 2. <input type="checkbox"/> Ոչ
10.	Ինչպիսի՞ն է ձեր ամուսնական կարգավիճակը: (Կարդացեք պատասխանները)	1. <input type="checkbox"/> Ամուսնացած 2. <input type="checkbox"/> Չամուսնացած 3. <input type="checkbox"/> Այրի 4. <input type="checkbox"/> Ամուսնալուծված
2.1.1 Ծխելը		
11.	Երբևէ ծխախոտ ծխե՞լ եք:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ, => Անցնել հարց #14
12.	Դուք ներկայումս ծխո՞ւ մ եք:	1. <input type="checkbox"/> Այո, ամեն օր 2. <input type="checkbox"/> Այո, ոչ ամեն օր, => Անցնել հարց #14 3. <input type="checkbox"/> Ոչ, => Անցնել հարց #14
13.	Միջինում, օրական քանի՞ գլանակ եք ծխում:	_____ գլանակ
2.1.2 Ալկոհոլի օգտագործում		
14.	Միջինում, որքա՞ն հաճախ եք գործածում ալկոհոլ պարունակող ըմպելիքներ: (Կարդացեք պատասխանները և բացատրեք, որ մեկ բաժին է մի բաժակ գինին կամ մի շիշ գարեջուրը կամ մի ըմպանակ լիկյորը, կոնյակը կամ օղին)	1. <input type="checkbox"/> Երբեք 2. <input type="checkbox"/> ամիսը 1 բաժնից քիչ 3. <input type="checkbox"/> ամիսը 1-3 բաժին 4. <input type="checkbox"/> 1-3 բաժին մեկ շաբաթում 5. <input type="checkbox"/> 4-6 բաժին մեկ շաբաթում 6. <input type="checkbox"/> 7-13 բաժին մեկ շաբաթում 7. <input type="checkbox"/> 14 և ավելի բաժին մեկ

2.2 Հայր		
15.	Խնդրում եմ նշել երեխայի հոր ծննդյան տարեթիվը.	_____ (տարի)
16.	Ի՞նչ կրթություն ունի երեխայի հայրը: <i>(Գարդացեք պատասխանները)</i>	1. <input type="checkbox"/> Դպրոց (9 տարի կամ պակաս) 2. <input type="checkbox"/> Դպրոց (10-12 տարի) 3. <input type="checkbox"/> Միջին մասնագիտական կրթություն 4. <input type="checkbox"/> Ինստիտուտ/համալսարան 5. <input type="checkbox"/> Հետդիպլոմային
17.	Այս երեխայով Ձեր հղիանալուն նախորդող 24 ամիսների ընթացքում Ձեր ամուսինն զբաղվե՞լ է հետևյալ աշխատանքներով. <i>(Գարդացեք պատասխանները)</i>	1. <input type="checkbox"/> Գյուղատնտեսական աշխատանք 2. <input type="checkbox"/> Էլեկտրիկ 3. <input type="checkbox"/> Վարորդ 4. <input type="checkbox"/> Մեխանիկ 5. <input type="checkbox"/> Այլ → մանրամասնեք _____
2.2.1 Ծիւելը		
18.	Նա երբևէ ծխախոտ ծխե՞լ է:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ => <i>Անցնել հարց #22</i>
19.	Նա ներկայումս ծխու՞մ է:	1. <input type="checkbox"/> Այո, ամեն օր 2. <input type="checkbox"/> Այո, ոչ ամեն օր, => <i>Անցնել հարց #21</i> 3. <input type="checkbox"/> Ոչ, => <i>Անցնել հարց #21</i>
20.	Միջինում, օրեկան քանի՞ գլանակ է ծխում:	_____ գլանակ
2.3 Ընտանեկան		
21.	Ձեր ընտանիքի անդամներից քանի՞ սն են ծխախոտ ծխում:	_____
22.	Մինչև երեխայի հիվանդանալը, որքա՞ն հաճախ էին մարդիկ ծխում երեխայի ներկայությամբ՝ նույն սենյակում:	1. <input type="checkbox"/> Ամեն օր 2. <input type="checkbox"/> Ոչ ամեն օր 3. <input type="checkbox"/> Երբեք
23.	Ձեր հղիության ընթացքում և երեխայի ծնվելուց հետո եղե՞լ է ժամանակ, երբ Ձեր ընտանիքի անդամներից որևէ մեկը գրեթե ամեն օր խմել է ոգելից խմիչքի 5 և ավելի բաժին (օրինակ՝ 5 բաժակ գինի կամ 5 շիշ գարեջուր կամ 5 փոքր բաժակ կոնյակ, օղի կամ լիկյոր):	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ 3. <input type="checkbox"/> Չգիտեմ/վստահ չեմ

24.	Ձեր ընտանիքի անդամներից կամ երեխայի մոտիկ ազգականներից (տատիկ, պապիկ, հորաքույր, հորեղբայր, մորաքույր, քեռի) որևէ մեկի մոտ երբևէ ախտորոշվե՞լ է քաղցկեղ:	1. <input type="checkbox"/> Այո → 1.1 Ազգակցական կապը երեխայի հետ _____ 2. <input type="checkbox"/> Ոչ
25.	Դուք ունե՞ք արդյոք որևէ արյունակցական կապ Ձեր ամուսնու հետ:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
26.	Երեխայի տատիկ-պապիկներից որևէ մեկն ունեցե՞լ է արյունակցական կապ իրար հետ:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
3. Երեխայի առողջական վիճակը		
27.	Որքա՞ն է եղել երեխայի քաշը ծնվելիս: (<i>Կարդացե՛ք պատասխանները</i>)	1. <input type="checkbox"/> 2500 գրամից քիչ 2. <input type="checkbox"/> 2500-ից 4000 գրամ 3. <input type="checkbox"/> 4000 գրամից ավել 4. <input type="checkbox"/> չեմ հիշում
28.	Այս երեխան ո՞րերորդ երեխան է Ձեր ընտանիքում:	_____(ին)րդ
29.	Երեխան ունեցե՞լ է արդյոք բնածին արատ:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
30.	Ծննդյան առաջին տարում երեխայի մոտ քանի՞ անգամ է ախտորոշվել որևէ ինֆեկցիոն հիվանդություն՝ ներառյալ գրիպը կամ այլ վիրուսային հիվանդություն: (<i>եթե ոչ մի՝ նշել 0</i>)	_____ անգամ
31.	Երեխան ունեցե՞լ է արդյոք որևէ խրոնիկ հիվանդություն՝ մինչև ներկա հիվանդությամբ հիվանդանալը:	1. <input type="checkbox"/> Այո => 1.1 <i>եթե այո, ապա ի՞նչ հիվանդություն</i> _____ 2. <input type="checkbox"/> Ոչ
32.	Երեխան անցե՞լ է որևէ ռենգտեն քննություն՝ նախքան հիվանդանալը:	1. <input type="checkbox"/> Այո => 1.1 <i>եթե այո, քանի՞ անգամ</i> _____ 2. <input type="checkbox"/> Ոչ

4. Հղիության ընթացքի վերաբերյալ		
33.	Ինչպե՞ս եք ծննդաբերել երեխային: <i>(Կարդացե՛ք պատասխանները)</i>	1. <input type="checkbox"/> Հեշտոցային/բնական ճանապարհով 2. <input type="checkbox"/> Կեսարյան հատումով
34.	Հղիության ո՞ր ամսում եք ծննդաբերել երեխային:	1. _____ (ամիս) 2. <input type="checkbox"/> Չեմ հիշում
35.	Մոտավորապես ինչքա՞ն էր Ձեր քաշն այս երեխայով հղիանալուց անմիջապես առաջ:	1. <input type="checkbox"/> _____ կգ 2. <input type="checkbox"/> Չգիտեմ
36.	Ինչքա՞ն է ձեր հասակը:	1. <input type="checkbox"/> _____ սմ 2. <input type="checkbox"/> Չգիտեմ
37.	Երբևէ կերակրե՞լ եք Ձեր երեխային կրծքի կաթով	1. <input type="checkbox"/> Այո, => 1.1 Եթե այո, քանի՞ ամիս _____ կամ քանի՞ _____ շաբաթ 2. <input type="checkbox"/> Ոչ
38.	Այս երեխայով հղիության ընթացքում ֆոլաթթու ընդունե՞լ եք:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
39.	Այս երեխայով հղիության ընթացքում սուրճ խմե՞լ եք: <i>(Կարդացե՛ք պատասխանները)</i>	3. <input type="checkbox"/> Այո, ամեն օր => 1.1 Օրեկան քանի՞ բաժակ _____ 4. <input type="checkbox"/> Այո, ոչ ամեն օր 3. <input type="checkbox"/> Ոչ
40.	Օգտագործե՞լ եք ալկոհոլ պարունակող խմիչքներ այս երեխայով հղիության ընթացքում: <i>(Կարդացե՛ք պատասխանները)</i>	3. <input type="checkbox"/> Այո, ամեն շաբաթ կամ ավելի հաճախ 4. <input type="checkbox"/> Այո, ոչ ամեն շաբաթ 3. <input type="checkbox"/> Ոչ
41.	Այդ հղիության ընթացքում միջինը քանի՞ անգամ եք սոնոգրաֆիա/ուլտրաձայնային քննություն անցել: <i>(եթե ոչ մի՝ նշել 0)</i>	_____
42.	Այդ հղիության ընթացքում ռենգտեն քննություն անցել ե՞ք:	1. <input type="checkbox"/> Այո, => 1.1 Քանի անգամ? _____ 2. <input type="checkbox"/> Ոչ → Անցնել #44
43.	Այդ հղիության ո՞ր եռամսյակում եք անցել ռենտգեն քննություն <i>(նշե՛ք բոլորը պատասխանները, որոնք համապատասխանում են):</i>	1. <input type="checkbox"/> Առաջին 2. <input type="checkbox"/> Երկրորդ 3. <input type="checkbox"/> Երրորդ
44.	Այդ հղիության ընթացքում հակաբիոտիկներ ընդունե՞լ եք:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ

45.	Որևէ հիվանդություն տարե՞լ եք այդ հղիության ընթացքում:	1. <input type="checkbox"/> Այո, → <i>1.1 Բնչ հիվանդություն</i> _____ 2. <input type="checkbox"/> Ոչ		
46.	Դուք ընդունե՞լ եք հակաբեղմնավորիչ հաբեր նախքան այս երեխայով հղիանալը:	1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ		
47.	Մինչև այս երեխայով հղիանալը ունեցե՞լ եք, արդյոք, վիժումներ:	1. <input type="checkbox"/> Այո => 1.1 Քանի՞ անգամ _____ 2. <input type="checkbox"/> Ոչ		
48.	Մինչև այս երեխայով հղիանալը կատարե՞լ եք, արդյոք, արբորներ:	1. <input type="checkbox"/> Այո => 1.1 Քանի՞ անգամ _____ 2. <input type="checkbox"/> Ոչ		
49.	Այս երեխայով հղիության ընթացքում ապրե՞լ եք ծանր սթրեսային վիճակ, օրինակ, հետևյալ իրավիճակներից որևէ մեկը՝ <i>(կարդացեք պատասխանները, և նշեք բոլոր համապատասխանող տարբերակները)</i>	1. <input type="checkbox"/> Բնական աղետ (երկրաշարժ, ջրհեղեղ, հրդեհ)	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ
		2. <input type="checkbox"/> Ձեր հանդեպ բռնություն (օր. ծեծ, բռնաբարություն, դանակահարություն, գնդակահարություն)	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ
		3. <input type="checkbox"/> Ձեր կյանքին վտանգ սպառնացող իրադարձություն (օր. վթար)	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ
		4. <input type="checkbox"/> Միբեղի մարդու հանկարծակի մահ	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ
		5. <input type="checkbox"/> Ձեր կամ Ձեր հարազատի մասնակցություն պատերազմական գործողության	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ
		6. <input type="checkbox"/> Այլ սարսափազդու իրադարձություն → 7. Խնդրեմ, մանրամասնեք _____	<input type="checkbox"/> Այո	<input type="checkbox"/> Ոչ

50.	<p><i>(Հարցրեք միայն այն մայրերին, ովքեր նշել են երբևէ ծխելու մասին)</i></p> <p>Ի՞նչ հաճախականությամբ եք ծխել այս երեխայով հղիության ընթացքում: <i>(Կարդացեք պատասխանները)</i></p>	<p>1. <input type="checkbox"/> Ամեն օր</p> <p>2. <input type="checkbox"/> Ոչ ամեն օր</p> <p>3. <input type="checkbox"/> Երբեք</p>
51.	<p>Այս երեխայով հղիության ժամանակ որքա՞ն հաճախ են մարդիկ ծխել Ձեր ներկայությամբ՝ նույն սենյակում: <i>(Կարդացեք պատասխանները)</i></p>	<p>1. <input type="checkbox"/> Ամեն օր</p> <p>2. <input type="checkbox"/> Ոչ ամեն օր</p> <p>3. <input type="checkbox"/> Երբեք</p>
5. Արտաքին միջավայրի ազդեցություններ		
52.	<p>Ձեր տանն ի՞նչ ջուր եք օգտագործում խմելու համար:</p>	<p>1. <input type="checkbox"/> Ծորակի ջուր</p> <p>2. <input type="checkbox"/> Ջրհորի ջուր</p> <p>3. <input type="checkbox"/> Շշալցված ջուր</p> <p>4. <input type="checkbox"/> Ֆիլտրված ջուր</p>
53.	<p>Ունե՞ք տնամերձ հողամաս/այգի, որտեղ թունաքիմիկատներ եք կիրառում:</p>	<p>1. <input type="checkbox"/> Այո</p> <p>2. <input type="checkbox"/> Ոչ => Անցնել #58</p>
54.	<p>Տարեկան միջինում քանի՞ անգամ եք Ձեր այգում կիրառում (փչում) թունաքիմիկատներ:</p>	<p>_____</p>
55.	<p>Ո՞վ է սովորաբար այդ թունաքիմիկատները կիրառում (փչում):</p>	<p>1. <input type="checkbox"/> Դուք (մայրը)</p> <p>2. <input type="checkbox"/> Հայրը</p> <p>3. <input type="checkbox"/> Այլ աշխատող</p>
56.	<p>Որքա՞ն հաճախ է երեխան ներկա գտնվել այդ (թունաքիմիկատներ կիրառելու) ընթացքում:</p>	<p>1. <input type="checkbox"/> Հաճախ</p> <p>2. <input type="checkbox"/> Երբեմն</p> <p>3. <input type="checkbox"/> Երբեք</p>
57.	<p>Լվանու՞մ եք մրգերը հոսող ջրի տակ՝ մինչև երեխային տալը (լինի դա Ձեր այգուց թե այլ տեղից ձեռք բերված), կամ երեխան ինքը լվանու՞մ է մրգերը՝ մինչև ուտելը:</p>	<p>1. <input type="checkbox"/> Այո</p> <p>2. <input type="checkbox"/> Ոչ</p>

58.	Քանի՞ տարի առաջ է ձեր բնակարանը/տունը կառուցվել (<i>եթե չի հիշում, մոտավոր թիվը հարցրեք</i>)	_____ տարի
59.	Հիմնականում ինչպե՞ս է ջեռուցվում Ձեր տունը: (<i>Կարդացեք պատասխանները</i>)	<ol style="list-style-type: none"> 1. Տաք ջրով (օրինակ՝ Բաքսի) 2. Էլեկտրական վառարանով 3. Ծխնելույզով վառարանով, որն այրում է գազ, նավթ կամ կերոսին 4. Փայտի կամ ածուխի վառարանով (ծխնելույզով) 5. Աթարի վառարանով 6. Անծխնելույզ վառարանով՝ նավթավառ, “ֆուջիկա” 7. Օջախով 8. Այլ կերպ (նշեք) _____ 9. Չի ջեռուցվում
60.	Ինչպե՞ս կգնահատեք Ձեր տան կենցաղային պայմանները: (<i>Կարդացեք պատասխանները</i>)	<ol style="list-style-type: none"> 1. <input type="checkbox"/> Լավ 2. <input type="checkbox"/> Միջին (բավարարում է հիմնական պահանջները) 3. <input type="checkbox"/> Վատ 4. <input type="checkbox"/> Այլ _____
61.	Ձեր բնակության վայրից մինչև 10 կմ հեռավորության վրա կա՞, արդյոք, քիմիական գործարան:	<ol style="list-style-type: none"> 1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
62.	Ձեր բնակության վայրից մինչև 10 կմ հեռավորության վրա իրականացվո՞ւմ է, արդյոք, որևէ հանքարդյունաբերություն:	<ol style="list-style-type: none"> 1. <input type="checkbox"/> Այո 2. <input type="checkbox"/> Ոչ
Հարցազրույցի ավարտ __ : __ (ժամ:րոպե)		

Շնորհակալություն!