

# Risk Factors for Malignancies in Pediatric Population: Results of A Population-Based Case-Control Study

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## Research Article

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# Abstract

Cancer is the most common cause of disease-related deaths in childhood. Many sociodemographic, socioeconomic, environmental and genetic risk factors have been associated with a childhood cancer risk. However, few to no such studies have been conducted in the Middle East including Lebanon.

This is a population-based case-control study that was conducted in the Lebanese pediatric population. Data was collected through face-to-face interviews, using a questionnaire, with parents of children with cancer in Lebanese pediatric cancer centers over a two-year period. In total, the sample consisted of 322 participants.

Results showed that there are several sociodemographic, socioeconomic, environmental factors, in addition to consanguinity between parents, level of education and occupation of the parents, area of residence of the child (location and proximity to high-voltage electrical networks, garbage disposal areas, industrial factories and high-ways) as well as sibling history of cancer are risk factors for childhood cancers in Lebanon.

**Conclusion:** This study informs policy makers on the risk factors in order to find solution as well as policies to decrease and mitigate these risks.

## What Is Known - What Is New (Author'S Summary)

### *What is known*

- Lebanon has a high annual incidence of childhood cancer and it is on the rise.
- There is scarce and limited evidence about the risk factors associated with childhood cancer
- Studies have shown that some sociodemographic, socio economic, environmental and genetics factors may be risk factors for childhood cancers

### *What is new*

- This study is the first Study of its kind in the Eastern Mediterranean Region
- Results of this study showed that risk factors that significantly increase odds of cancer in children include, consanguinity between parents, level of education of the parents, occupation of the mother, area of residence of the child (location and proximity to high-voltage electrical networks, garbage disposal areas, industrial factories and high-ways) as well as sibling history of cancer.
- Study informs policy makers on the risk factors associated with an increased risk of cancer in children below age of 19 years in order to find solution as well as policies to decrease and mitigate the risks.

## Introduction

Cancer is the most common cause of disease-related deaths in childhood, carrying a great economic and emotional cost.<sup>1</sup> Concern has been raised in the United States and Europe that the overall rates of childhood cancer have been on the rise since the 1970s.<sup>2</sup> The incidence of cancer in children worldwide is about 16.4 per 100,000.<sup>3</sup> If these worldwide statistics are alarming, the situation is no less worrisome in Lebanon; a population of 5 million has witnessed an increase in the number of children seeking care and treatment in Children's Cancer Centre Lebanon (CCCL) diagnosed with cancer from 7.6 cases in 100,000 in 2011, to 17.2 in 100,000 in 2016.<sup>4,5</sup> Furthermore, Leukemia was reported as one of the most common malignant neoplasms in childhood in Lebanon.<sup>6</sup> Although part of this increase may be due to improvement in cancer diagnosis and recording, this does not entirely explain the increase in the incidence of childhood cancer.<sup>7</sup> Various risk factors have been investigated in an attempt to elucidate the etiologies of cancer in children.<sup>8,9</sup> A direct association between sociodemographic, socioeconomic and environmental risk factors and an increased risk of developing cancer during childhood has been studied. Socioeconomic status has been linked to health outcomes in children, whereby lower socioeconomic status is linked with worse health outcomes.<sup>10</sup> These socioeconomic factors and living conditions can increase incidence of childhood cancer through mediators such as dietary patterns, residence area, parents' educational level, parents' occupation, family reproductive decisions (such as maternal age), etc.<sup>10</sup> Accordingly, all these factors fall under the notion on social determinants of health that have been known to lead health inequities within and between countries.<sup>11</sup> As such, these determinants are likely to risk for a disease such as cancer, or vulnerability to disease or injury for people of lower socioeconomic status.<sup>12</sup> This is true for Lebanon, as studies have shown that social determinants of health had lead disparities across gender, income, educational level, governorates, physical environments and employment/working conditions.<sup>13</sup>

Inherited genetic mutations play role in about 10% of all cancers. Research studies have associated inherited genetic mutations with more than 50 types of hereditary cancers.<sup>14</sup> Certain types of cancer seem to run in some families and studies have shown that family history (first and second degree family members) of some types of cancer such as colorectal cancer and breast-ovarian cancer are associated with a significant increased risk of cancer in individuals.<sup>15</sup>

## **Clinical Significance**

Based on the aforementioned, a multitude of various research studies have examined a number of potential risk factors, in an effort to determine the etiology of malignancies, but the evidence for causal association is still in the preliminary stages. In addition, according to our knowledge no such studies have been done in Lebanon to determine the potential risk factors of childhood cancers. Therefore, this study comes as an attempt to fill this gap in the literature. Furthermore, from a population perspective, the prevalence and incidence of cancer cases among children as measure of association are as important as the search for potential risk factors as it would allow us to determine the basis for preventive measures required to keep the number of childhood cancer cases in check. In light of the on-going increase in

incidence of childhood cancer in Lebanon a case-control study to determine the associations between childhood cancer and sociodemographic, socioeconomic, environmental and genetic risk factors is highly warranted. Similar to other research on this subject <sup>16,17,18</sup>, this study aims to inform policy makers on the risk factors associated with an increased risk of cancer in children below age of 19 years in order to find solution as well as policies to decrease and mitigate the risks.

## Objectives of the Study

This study has the following main objectives:

1. Identify and explore the risk factors (sociodemographic, socioeconomic, environmental and genetic) that increase risk cancers in children in Lebanon.
2. Inform policy through evidence based data on the risk factors that increase odds of childhood cancers

## Material And Methods

### Conceptual Framework of the Study

The below figure (Fig. 1) describes the conceptual framework of this study.

### Study Design and Survey Questionnaire

A case-control study was conducted in the Lebanese pediatric population. Data was collected through face- to-face interviews, using a questionnaire, with parents of children with cancer in Lebanese pediatric cancer centers over a two-year period. Furthermore, whenever available, medical charts were used to validate the information obtained from the parents during the interviews. This was done due to the fact that data obtained from medical charts are considered more valid than those obtained orally from parents, which may be affected by recall bias and social desirability bias.

The detailed and comprehensive questionnaire used for data collection was divided into four sections:

- The first section gathers general information about the family in which the child (case/control) has been raised, including consanguinity, socio-economic factors and family exposure to environmental factors.
- The second section focuses on the case/control life history from conception, including lifestyle habits and exposures.
- The third section focuses on the mother's occupational and environmental exposures, and reproductive history.
- The fourth section focuses on the father's occupational and environmental exposures and reproductive history.

Several steps were taken in order to validate the questionnaire. Initially, the Questionnaire was built in English, translated to Arabic and then translated back to English for accuracy. After that, it was piloted in a group of 10 individuals before it was finalized. The questionnaire was filled out in either Arabic or English based on the participants' preference.

## Study Sample

Patients were selected from pediatric wards in the four university hospitals in Greater Beirut (Saint Jude Cancer Center, American University of Beirut-Medical Center, Hariri General Hospital, Makassed General Hospital and Saint Georges Hospital.), which tend to drain the largest case-load of diseases of all types from all regions and all socioeconomic strata. Cases were selected from the list of patients available for all health care professionals at the hospitals and cancer centers with no prior criteria except for the study inclusion and exclusion criteria. This list included the patients' ages and type of malignancy. Access to the list of cases was obtained after informing the head nurse on the pediatric oncology floor. Likewise, controls were selected from the list of patients available for all health care professionals at the pediatric ward of the four hospitals. This list included the patients' ages and diagnosis. After selecting cases and controls from the list with respect to inclusion/exclusion criteria, the head nurse's approval was also obtained to interview children parents' in their rooms. Selection of cases and controls was based over a period of time due to its convenience; ease of use as well as to ensure that there is a more accurate representation of the larger pediatric population Lebanon. The aim of the interview and the goal of the study were explained to the parents. The parents were also informed that their participation in this study is completely voluntary.

## Sample size calculation

The number of cases, which could have been recruited into this study, is limited by the actual caseload of pediatric cancers in Lebanon, which is about 200 new cases per year<sup>4</sup>. Therefore, the number of cases to be selected has been arbitrarily determined at about half all incident cases over a two-year period; i.e., 200 cases. Controls are usually more abundant than cases, and therefore a ratio of 2 controls to 1 case has been selected to increase the power of the study. Consequently, the total number of participants was expected to be about 600 children. The parents of more than 650 children were contacted, but only around half of them agreed to participate in this study. The final total number of those who agreed to participate in this study is 322, with a ratio of 2 controls to 1 case in order to increase the power of the study (137 cases and 185 controls).

## Inclusion and Exclusion Criteria

### Cases

Included cases were children aged  $\leq 19$  years, diagnosed with cancer within duration of 2 years or less, alive at the time of the study, receiving all the treatment in Lebanon and whose parents voluntarily agreed

to participate in the study. The cases were recruited from the aforementioned pediatric cancer centers and hospitals.

## Controls

After cases were identified, controls were selected through a procedure of frequency group matching by current area of residence and by 3-year age groups. Controls were selected equally and sequentially from all four hospitals, until numbers require for all residence-age subgroups have been fulfilled. To be eligible, a control must satisfy the following criteria: not suffering from cancer, residing in Lebanon, disability, or any chronic condition; no cancer cases among siblings, and parents willing to participate.

## Statistical analysis

All variables were entered and analyzed using SPSS software (version 19.0). Categorical variables are presented as frequencies and percentages; while continuous variables are presented with means, standard deviations (SD), medians and intervals. For the needs of the analysis, continuous variables will be divided into categories on cut-offs which vary for each particular variable. Similarly, several variables measuring the same concept may be summarized into one index, which will also be subsequently categorized. The dependent variable is disease status: case versus controls. The association between all independent variables and the disease status was measured using the odds-ratio (OR) and its 95% confidence interval (95% CI) and a p-value (set at  $\leq 0.05$ ). Since this study is a retrospective case-control, study OR will be used to measure the strength of association between the risk factors and cancer in children and as rough approximate for the Relative Risk (RR).

## Ethical Considerations

The study obtained approvals from the research committee at LAU School of Pharmacy, and the IRBs of the concerned hospitals. This study was performed in accordance with the principles set forth in the Declaration of Helsinki and the three basic principles of the Belmont Report (respect of persons, beneficence and justice). Furthermore, the data was aggregated, analyzed and used for the purposes of academic research and statistical analysis only. The study did not cause any harm, direct or indirect, to the parents nor to the patients and no direct identifiers were at any point collected in this research study.

## Results

### Socioeconomic characteristics

In total, 332 participants (mother or father of child) agreed to participate in the survey and gave complete information. Most of the surveyed participants were 0–9 years of age ( $n = 192, 59.67\%$ ), 83 participants in the cases groups and 110 participants in the control, group (Table 2). While there were around 129 participates whose ages ranged between 10–19 years (54 cases and 75 controls). The majority of the in the control and cases groups were Muslim ( $n = 198, 68\%$ ), 24.4% were Christian ( $n = 71$ ) while only 7.6%

were Druze (n = 22). Around 31 refused to answer this question; that is why total number of participants appears as 291 in Table 1. More than half of the surveyed participants were males (n = 176, 54.7%). The number of females and males in both in the cases and controls groups were similar. There was no significant difference between the genders in both groups (p = 0.897).

Table 1  
Demographic characteristic of the Participants

<i>Variable</i>	<i>Category</i>	<i>Cases</i>	<i>Control</i>	<i>Total</i>
<i>Age</i>	0–9 years	83(44%)	110 (66%)	<b>193</b>
	10–19 years	54(41.8%)	75(58.2%)	<b>129</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Gender</i>	Female	60 (41%)	86 (59%)	<b>146</b>
	Male	77 (43.75)	99 (56.25%)	<b>176</b>
	Total	137	185	<b>322</b>
<i>Religion</i>	Muslim	86 (43.4%)	112 (56.6%)	<b>198</b>
	Christian	25 (35.2%)	46 (64.8%)	<b>71</b>
	Druze	7 (31.8%)	15 (68.2%)	<b>22</b>
	Total	<b>118</b>	<b>131</b>	<b>291</b>

Table 2  
Sociodemographic and socioeconomic factors

<i>Variable</i>		<i>Cases</i>	<i>Control</i>	<i>Total</i>
<i>Consanguinity between parents</i>	No	102 (39.8%)	154 (60.2%)	<b>256</b>
	Yes	35 (53%)	31 (47%)	<b>66</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Mother's education level</i>	Less than Primary	33 (84.6%)	6 (15.4%)	<b>39</b>
	Less than Brevet	24 (55.8%)	19 (44.2%)	<b>43</b>
	Brevet	31 (50%)	31 (50%)	<b>62</b>
	Bacc	24 (33.3%)	48 (66.7%)	<b>72</b>
	Post-Bacc (high school degree and beyond )	24 (22.9%)	81 (77.1%)	<b>105</b>
	Total	<b>136</b>	<b>185</b>	<b>321</b>
<i>Father's education level</i>	Less than Primary	29 (72.5%)	11 (27.5%)	<b>40</b>
	Less than Brevet	22 (53.7%)	19 (46.3%)	<b>41</b>
	Brevet	24 (57.1%)	18 (42.9%)	<b>42</b>
	Bacc	31 (45.6%)	37 (54.4%)	<b>68</b>
	Post-bacc (high school degree and beyond )	29 (22.8%)	98 (77.2%)	<b>127</b>
	Total	<b>135</b>	<b>183</b>	<b>318</b>
<i>Father occupation</i>	Painting	2 (66%)	1(34%)	<b>3</b>
	Industrial	12(92%)	1(8%)	<b>13</b>
	Trade	17(32.6%)	35 (67.4%)	<b>52</b>
	Services	71(38.7%)	112(61.3%)	<b>183</b>
	Education	10(50%)	10(50%)	<b>20</b>
	Agriculture	2(50%)	2(50%)	<b>4</b>
	Military	11(68.75%)	5(31.25%)	<b>16</b>
	Driver	5(33%)	10(67%)	<b>15</b>
	Gas Station	3(60%)	2(40%)	<b>5</b>
	Unemployed	2(28.5%)	5(71.6%)	<b>7</b>

<i>Variable</i>		<i>Cases</i>	<i>Control</i>	<i>Total</i>
	Total	135	183	<b>318</b>
<i>Mothers occupation</i>	Homemakers	126 (48.8%)	132 (51.2%)	<b>258</b>
	External Employee	10 (16.1%)	52 (83.9%)	<b>62</b>
	Total	<b>136</b>	<b>184</b>	<b>320</b>

## Sociodemographic Socioeconomic characteristics

A sizeable proportion of the participants had non-consanguineous parents ( $n = 256, 79.5\%$ ) while only 20.5% had consanguineous parents with the majority being second-degree relatives (cousins). More reported consanguinity between parents in the cases than in the control group ( $n_{cases} = 35, n_{control} = 31$ ). The OR was 2.915. So the children of consanguineous parents are significantly at some higher odds of having cancer during childhood ( $p\text{-value} = 0.001, CI\ 95\% [1.555\ to\ 5.464]$ ).

Around one third of the children's mothers had a post Lebanese Baccalaureate degree ( $n = 105$ ), of whom were in the control group ( $n = 81, 77.1\%$ ). However, around 44% ( $n = 151$ ) of the mother had a Brevet degree (grade 9) or lower level of education (Table 2). OR was calculated to be OR 18.563, so children whose mother have a less than primary level of education have significantly greater odds of cancer than the children whose mothers had a post-bacc education (high school degree and beyond) ( $p\text{-value} = 0.000, CI\ 95\% [6.953\ to\ 49.553]$ ). Table 2 presents the different levels of the fathers' education in the control and the cases. The odds of cancer in children whose fathers have less than a primary education are 8.909 significantly more than the children whose fathers had a post-bacc education (high school degree and beyond) ( $p\text{-value} = 0.000, CI\ 95\% [3.97\ to\ 19.993]$ ).

Children whose mother have a less than primary level of education have significantly greater odds of cancer than the children whose mothers had a post-bacc degree (high school degree and beyond) ( $p\text{-value} = 0.000, CI\ 95\% [6.953\ to\ 49.553]$ ). Four participants refused to answer the question pertaining to the Father educational level ( $n = 318$ ) and two refused to answer what the question relate to the mother educational level ( $n = 320$ ).

More than half of the fathers worked in the services sector ( $n = 138, 56.1\%$ ). The rest worked in various fields such as education, military, transportation etc. (Table 2). Only 2.2% of the fathers were unemployed ( $n = 7$ ). Father's occupation; regardless of the sector was not significantly associated with an increased odds (OR = 1.868) of cancer in their children ( $p\text{-value} = 0.715, CI\ 95\% [0.357\ to\ 9.777]$ ).

The vast majority of mothers were homemakers ( $n = 281, 80.1\%$ ), while only 19.3 % ( $n = 62$ ) of mothers had a full time job in the workforce (Table 2). The OR (odds of mother being an external employee in cases vs. odds of mother being an external employee in control) was 0.201 (Chi-squared 20.566) and it was significant ( $p\text{-value} = 0.00000, CI\ 95\% [0.098\ to\ 0.414]$ ). Four participants and two participants did

not answer the question on the Father's occupation (n = 318) and mother's occupation (n = 320) respectively.

## **Residence History and Details**

About one third of the participants resided in Beirut, the capital city of Lebanon (n = 116). The residence areas of the participants were as follows: 75 participants in the North of Lebanon, 51 participants in Mount Lebanon, 46 participants in South of Lebanon, 25 participants in the Bekaa region and only participants in the Metn Area. Most of the participants lived in urban and suburban areas (Table 3). About 61 participants stated that they live in rural areas. There was one participant who lived in a refugee camp. Children who live in urban and suburban areas were at a significantly greater odds of cancer than those who live in rural and semi-rural areas (OR=, 9.43 p-value = 0.0000, CI 95% [0.053 to 0.214]).

Table 3  
Residence Details

<b>Variable</b>	<b>Category</b>	<b>Case</b>	<b>Control</b>	<b>Total</b>
<i>Residence Area</i>	Beirut	36 (31%)	80 (69%)	<b>116</b>
	South	25 (54.3%)	21 (45.7%)	<b>46</b>
	North	35 (46.7%)	40 (53.3%)	<b>75</b>
	Bekaa	15 (60%)	10 (40%)	<b>25</b>
	Mount Lebanon	22 (43.1%)	29 (56.9%)	<b>51</b>
	Metn	4 (44.4%)	5 (55.6%)	<b>9</b>
	<b>Total</b>	<b>137</b>	<b>185</b>	<b>322</b>
<i>Type of area of residency</i>	Urban	33 (34.4%)	63 (65.6%)	<b>96</b>
	Suburban	27 (26.5%)	75 (73.5%)	<b>102</b>
	Semi-rural	27 (43.5%)	35 (56.5%)	<b>62</b>
	Rural	49 (80.3%)	12 (19.7%)	<b>61</b>
	Camp	1 (100%)	0 (0%)	<b>1</b>
	<b>Total</b>	<b>137</b>	<b>185</b>	<b>322</b>
<i>Agricultural area</i>	No	89 (37.1%)	151 (62.9%)	<b>240</b>
	Yes	48 (58.5%)	34 (41.5%)	<b>82</b>
	<b>Total</b>	<b>137</b> (42.5%)	<b>185</b> (57.5%)	<b>322</b>
<i>Factory in the neighborhood</i>	No	109 (41.1%)	156 (58.9%)	<b>265</b>
	Yes	28 (49.1%)	29 (50.9%)	<b>57</b>
	<b>Total</b>	<b>137</b>	<b>185</b>	<b>322</b>
<i>Highway proximity</i>	Less than 50 meters	22 (28.9%)	54 (71.1%)	<b>76</b>

<i>Variable</i>	<i>Category</i>	<i>Case</i>	<i>Control</i>	<i>Total</i>
	Between 50–100 meters	28 (26.2%)	79 (73.8%)	<b>107</b>
	Between 100–500 meters	87 (62.6%)	52 (37.4%)	<b>139</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Proximity to high voltage electrical networks</i>	No	113 (39.6%)	172 (60.4%)	<b>285</b>
	Yes	24 (64.9%)	13 (35.1%)	<b>37</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Proximity to garbage disposal areas</i>	Within smelling distance	16 (88.9%)	2 (11.1%)	<b>18</b>
	Within visual	9 (81.8%)	2 (18.2%)	<b>11</b>
	Both	14 (60.9%)	9 (39.1%)	<b>23</b>
	No	98 (36.3%)	172 (63.7%)	<b>270</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>

The vast majority stated that they lived in non-agricultural areas (ntotal = 240, ncases = 89, ncontrol = 151), while about a quarter (ntotal = 82) only stating that they live in agricultural areas (Table 3). The OR of living in a non-agriculture area versus living in an agricultural area was 0.417 (p-value = 0.001, CI 95% [0.25 to 0.696]).

On the other hand, less than a quarter lived in a neighborhood where there is an industrial factory (n = 57). However, children who had an industrial factory in their neighborhood had 1.382 times the odds of cancer than those who did not have a factory in their neighborhood, but this result was not significant (p-value = 0.337, CI 95% [0.778 to 2.453]).

When it comes to proximity to a highway, only 76 in total (ncases = 22, ncontrol = 54) stated that they have a highway less than 50 meters away from their home residence. On the other hand, about one thirds stated that they have a highway between 50–100 meters away from their home residence while the largest number of participants stated that the nearest highway to their home residence is between 100–500 meters. Children who lived less than 50 meters from a highway were at a significantly greater odds of cancer than those who lived between 100 and 500 meters from a highway (OR=, 4.107, p-value = 0.0000, CI 95% [2.247 to 7.506]).

The majority of participants (n = 258) did not have high voltage electrical networks near their home residence whereas only 37 said that they live near high-voltage electrical network (Table 3). The

calculated OR was 2.81, so children who lived near high voltage electrical networks had significantly higher odds of developing cancer as opposed to those who those who did not live near high voltage electrical networks (p-value = 0.006, CI 95% [1.374 to 5.747]).

Most of the surveyed participants (n = 270) did not have a garbage disposal area within proximity of their home residence, however around 8% (n = 23) of the participants had a garbage disposal site within smelling and visual distance from their home residence.

Only 18 said that they had a garbage disposal area within smelling distance of their home residence whereas merely 11 had a garbage disposal area within visual distance of their home residence (Table 3). Children who lived within smelling and visual proximity to garbage disposal areas had 2.73 the odds of having cancer as opposed to those who did not live within smelling and visual proximity to garbage disposal areas (p-value = 0.035, CI 95% [1.14 to 6.539]).

## **Family History of Malignancies**

Maternal history of malignancies was reported by two participants only, one in the control group and one in the case group. Whereas the vast majority in both groups denied any maternal history of malignancies (ncases = 134, ncontrol = 185) (Table 4). Children whose mothers had a history of malignancy had 1.35 more odds of developing cancer than those whose mothers had no history of malignancies. (OR = 1.35, Chi-squared 0.255). Yet the result were not significant as the observed p-value was great than 0.05 (p-value = 0.641, CI 95% [0.084 to 21.78]). Moreover, only five participants reported sibling history of malignancies all of whom are cases (ncases = 5, ncontrol = 0). The OR was 15.417, as such the odds of developing cancer in children whose siblings also have cancer is 15.417 times that of children whose siblings do not have cancer (p-value = 0.045, CI 95% [0.835 to 284.749]). Similarly, only two reported paternal history of malignancies one in the cases group and one in the control group (Table 4).

Table 4  
Family History of Malignancies

<b>Variable</b>	<b>Category</b>	<b>Case</b>	<b>Control</b>	<b>Total</b>
<i>Siblings with malignancies</i>	No	129 (41.1%)	185 (58.9%)	<b>314</b>
	Yes	5 (100%)	0 (0%)	<b>5</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Presence of malignancy in mother</i>	No	135 (42.3%)	184 (57.7%)	<b>319</b>
	Yes	1 (50%)	1 (50%)	<b>2</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>
<i>Presence of malignancy in father</i>	No	96(30.3%)	220(69.7%)	<b>316</b>
	Yes	1(50%)	1(50%)	<b>2</b>
	Total	<b>97</b>	<b>221</b>	<b>318</b>
<i>Presence malignancies among second degree relatives</i>	No	97 (39.9%)	146 (60.1%)	<b>243</b>
	Yes	37 (48.7%)	39 (51.3%)	<b>76</b>
	Total	<b>137</b>	<b>185</b>	<b>322</b>

Those participants whose fathers had a history of malignancies had 2.292 times the odds of childhood cancer than those whose fathers had no history of malignancies (OR2.292, Chi-squared0.029). However the result were not significant as the observed p-value was great than 0.05(p-value = 0.865, CI 95% [0.142 to 37.019]).

When it comes to presence malignancies among second-degree relatives (as in grandparents, uncles, aunts, first cousins etc.), 37 participants and 39 participants in the case group and control group respectively reported that a second-degree family member had (or currently has) a history of malignancies (Table 4). Children who had malignancies among second-degree relatives had 1.428 the odds of developing cancer as opposed to children whose second-degree relatives had no malignancies (OR 1.428, Chi-squared 1.484), but the result was not significant (p-value = 0.223, CI 95% [0.851 to 2.397]).

## Discussion

Childhood cancers are a rising global concern. Many studies have attempted to look at the risk factors that increase risk the off of cancer in the pediatric population. Similar to other research on risk factors for childhood cancers, this study revealed that a number of sociodemographic, socioenocmic, genetic and environmental risk factors that are associated with cancers in children.

Some of the sociodemographic and socioeconomic risk factors examined in this study and were consanguinity between parents, education level of both parents and the occupation of both parents. Consanguineous marriages have long been associated with an increased risk for a number of diseases such as autosomal recessive diseases and congenital malformations.<sup>19</sup> Additionally studies shown that in some Arab communities where there is a high rate of consanguinity, there is a significant increase in the prevalence of common non-communicable diseases like cancer.<sup>20</sup> This directly correlates to the findings of this study, which showed that consanguinity of parents significantly increases odds of cancer in their children. In addition, education level of the parents and its correlation to cancer incidence in their children has been the topic of debate in the past decade. Yet most studies looked at the correlation between the educational level of the parents and the child's cancer survival rate, whereby children whose parents had higher education (University) had a slightly significantly better survival rate.<sup>21</sup> These studies emphasized that the education level of the mother is more important than education level of the father.<sup>21,22</sup> Very few studies looked at the relationship between the education level of the parents and the risk of cancer in her children. From these, few studies it was revealed that the children of parents with lower level of education had a slightly increased risk of cancer.<sup>23</sup> Correspondingly, this was also observed in this study. The occupation of the mother has been thoroughly studied in order to determine if there is an association between a mother's occupation and an increased risk of cancer in her children. It has been hypothesized that a mother occupational exposure to certain chemical such as petroleum, solvents that contain chlorinated hydrocarbons, paints, and pesticides might affect childhood cancer in the offspring through genetic changes in the ovum and/or through trans-placental carcinogenesis.<sup>24,25</sup> In this study, the majority of the mothers were homemakers as such they are less likely to be exposed to the aforementioned chemicals and solvent, yet the occupation of the mother was shown to significantly increase the odds of her children developing cancer. Nevertheless, it should be noted that this association maybe due to confounders that were unmeasured and unaccounted for in our study such as family income, access to quality of pre-natal healthcare services etc. On the other hand the result of this study showed that a father's occupation did not significantly increase odds of cancer in his children. There is inconsistent data on this issue; however some studies were able to associate certain types of paternal occupational exposure such as exposure to radioactive material, lead, asbestos, cadmium etc., with an increased risk of cancer in his children.<sup>25,26,27</sup>

Environmental risk factors that were examined in this study were area of residence (urban vs. rural), and if living in proximity to high-voltage electrical networks, garbage disposal areas, industrial factories and highways or not. Existing literature suggests modest yet positive associations between urbanization and residential area and cancer incidence in all age population.<sup>28</sup> This is may be due to the high levels of air pollution in urban areas and exposure to all sorts of pollutants, chemicals etc. In this study, children who lived in urban and suburban areas were shown to have significantly higher odds of cancer. However, studies have shown that people of all age groups and specifically children living in urban areas are more likely to be screened for and diagnosed with cancer due to the fact that access to healthcare services in urban areas is much easier than in rural areas.<sup>29,30</sup> This is the case in Lebanon where the healthcare

system is highly fragmented, the private healthcare sector is dominant and the vast majority of healthcare institutions are located in urban areas namely the Greater Beirut Area.<sup>31</sup> Whereas in rural areas there are a limited number of healthcare facilities, most of them public and are unable to meet the health needs of the population living in those rural areas.<sup>32</sup>

Several studies have examined association between childhood cancers and living near high-voltage electrical networks, but no consistent evidence for an association between living near high-voltage electrical networks (or any source of non-ionizing Electromagnetic fields (EMF)) and cancer has been found.<sup>33</sup> Nevertheless, our results show that children living near high-voltage electrical networks have higher odds of developing cancer.

Results of this study suggest that children who lived in proximity to industrial factories were at higher odds of cancer as opposed to those who did not. Similarly, the literature suggests a possible positive association between living in proximity to certain industrial factories and risk of childhood cancer<sup>34</sup> ; however, more studies are necessary before establishing and confirming this relationship. Moreover, our findings show that children who lived in proximity to highways were at higher odds of cancer as opposed to those who lived far from highways (more than 500 meters). Likewise, reported studies show that children living in proximity of highways are exposed to higher concentrations of traffic-related carcinogenic pollutants and in turn they have an increased risk of childhood cancer, but the published evidence remains inconclusive.<sup>35,36</sup>

Possible associations between certain types of cancer such as for liver cancer, kidney cancer, pancreatic cancer, and non-Hodgkin's lymphomas and living close to garbage disposal sites/landfills have been studied yet the evidence is inconsistent.<sup>37,38,39</sup> In addition most of the studies on this subject looked the association between living close to garbage disposal sites/landfills and risk of cancer in adults (and not in children).<sup>40</sup> The finding of this study children living in garbage disposal areas/landfills are at higher odds of developing cancer. It should be noted that since 2015 Lebanon has been witnessing a waste management crisis with widespread dumping and burning of garbage/waste on the streets.<sup>41,42</sup> Human Rights Watch calls this crisis "a national health crisis".<sup>42</sup> Studies conducted by local research and environmentalists shows that there has been increase in cancer rates in the past couple of years in the Lebanese population at large as a results of the exposure garbage/waste on the streets that been dumped and burned on the streets since 2015.<sup>43,44</sup>

Lastly, this study looked at genetic risk factors such as were studied history of malignancy in parents, history of malignancy in siblings and history of malignancies in second degree family. Most cancers are not clearly linked to genetics and family history. However, certain types of cancer such as breast cancer, ovarian cancer, uterine cancer, colorectal cancer, melanoma, retinoblastoma and pancreatic cancer have been shown to run in some families.<sup>45,46</sup> In a study published in the New England Journal of Medicine, 8.5% of the children (below age of 18) with cancer were found to have germ line mutations in cancer-predisposing genes.<sup>15</sup> The results of this study highlighted that sibling history of cancer significantly led

to higher odds of cancer in children, but that history of cancer in both parents did not significantly increase odds of cancer in their children. This was also the case when it comes to history of malignancies in paternal and maternal second-degree family members (aunts, uncles, cousins etc.).

## **Study strength and limitations**

### **Strengths**

This study was the first of its kind in Lebanon to our knowledge. That being so the findings of this study can be used in future studies on the risk factors of childhood cancer in Lebanon and even in other low to middle income countries in the Eastern Mediterranean Region (EMR). Accordingly, this study can be a starting point to conducting a large wider scale study that examines a wider range of sociodemographic, socioeconomic, environmental and genetic risk factors risk factors for developing a childhood cancer. Additionally, the developed questionnaire can be used in future studies as it has been validated and translated to Arabic.

### **Limitations**

Since this study is a cross-sectional one, it has some limitations including; it only offers a snapshot of a single point in time and thus is not appropriate to establish causality between the different risk factors for childhood cancers. Additionally, recall bias might be a major drawback whereby participants do not remember previous events or experiences accurately or omit details (consciously or unconsciously). Recall bias can increase or decrease the strength of the observed associations. Overestimation of risk estimates due to recall bias is of concern particularly in studies of parental self-reporting of sociodemographic factors, children's exposures to infections, chemicals etc. and childhood cancer.<sup>47,48</sup> Furthermore, this study was limited to four privately owned tertiary hospitals located in the Greater Beirut Area. Finally, a significant limitation of this study is that analysis of the relationship between the aforementioned risk factors could not be performed to determine its association to specific subtypes of childhood cancers.

### **Areas for Future Research**

Longitudinal studies that assesses the impact of risk factors such as sociodemographic socioeconomic, social, genetic as well other social determinants of disease on the health of children particularly with regards to risk of malignancies and cancers are highly warranted. Thus, for future research, it is recommended that similar studies to be carried out across all 130 hospitals; both public and private in urban as well as in rural areas; across all the areas of Lebanon in order to obtain large sample sizes which will allow generalization of results on a national and regional level.

### **Policy implications**

The results of this study helps health policy makers and all governmental entities including (but not limited to) Ministry of Public Health, Ministry of Social Affairs, Ministry of Labor etc. identify public health

policy priorities. This study supports the need to improve access to healthcare services in rural areas, promote effective urban planning that takes into consideration placing hazardous elements such as industrial factories, high-voltage electrical network etc. away from populated residence areas and promote early and correct diagnosis of childhood cancer especially for children who lie in the high risk population (lower socioeconomic) particularly those who have a family (and sibling) history of cancer.

## Conclusion

In conclusion, in Lebanon the annual incidence of cancer in children is 17.0 in 100,000 and it is on the rise. There is scarce and limited evidence about the risk factors associated with childhood cancer in Lebanon and this study aimed to fill an existing gap in the literature. Consequently, this study aimed to examine risk factors for childhood cancers in Lebanon. These risk factors were sociodemographic, socioeconomic, environmental and genetics risk factors. Accordingly, based on the results, risk factors that significantly increase odds of cancer in children include, consanguinity between parents, level of education of the parents, occupation of the mother, area of residence of the child (location and proximity to high-voltage electrical networks, garbage disposal areas, industrial factories and high-ways) as well as sibling history of cancer. More studies preferably longitudinal ones are recommended in order to provide evidence about the etiology and potential risk factors for cancer in children in Lebanon. Finally this study highlights the need for public health policies that improve access to healthcare services in rural areas, promote effective urban planning promote early and correct diagnosis of childhood cancers.

## List Of Abbreviations

CCCL Children's Cancer Centre Lebanon

CI Confidence Interval

ER Eastern Mediterranean Region

OR Odds-Ratio

RR Relative Risk

SD Standard Deviation

## Declarations

### ***Declaration of conflicting interests***

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## ***Ethics approval***

The study obtained approvals from the IRB at the Lebanese American University(LAU), the research committee at LAU's School of Pharmacy, and the IRBs of the concerned hospitals. This study was performed in accordance with the principles set forth in the Declaration of Helsinki and the three basic principles of the Belmont Report (respect of persons, beneficence and justice).

## ***Consent to participate***

An informed consent was signed by participants prior to the interview. The form clearly indicates that participation is voluntary, that participants may stop the interview when they want at no cost for them, that they have the right not to answer any of the questions, and that data are treated anonymously and in aggregate. The study investigators subsequently contacted directly the consenting ones. Interviews were conducted on hospital premises. For every selected case, a control coming from the same area and within three years of age difference was selected directly from hospital departments not associated with oncology. Parents were met on premises to explain the aim and procedures and obtain consent prior to conducting the interview.

## ***Consent for publication***

N/A

## ***Availability of data and material***

Due to privacy and ethical concerns, neither the data nor the source of the data can be made available

## ***Code availability***

N/A

## ***Authors' Contributions***

The authors confirm contribution to the paper as follows: study conception and design: YS, RZ, SGN; data collection: YS. ; Analysis and interpretation of results: MN, YS, LS. Draft manuscript preparation: MN, YS. All authors reviewed the results and approved the final version of the manuscript.

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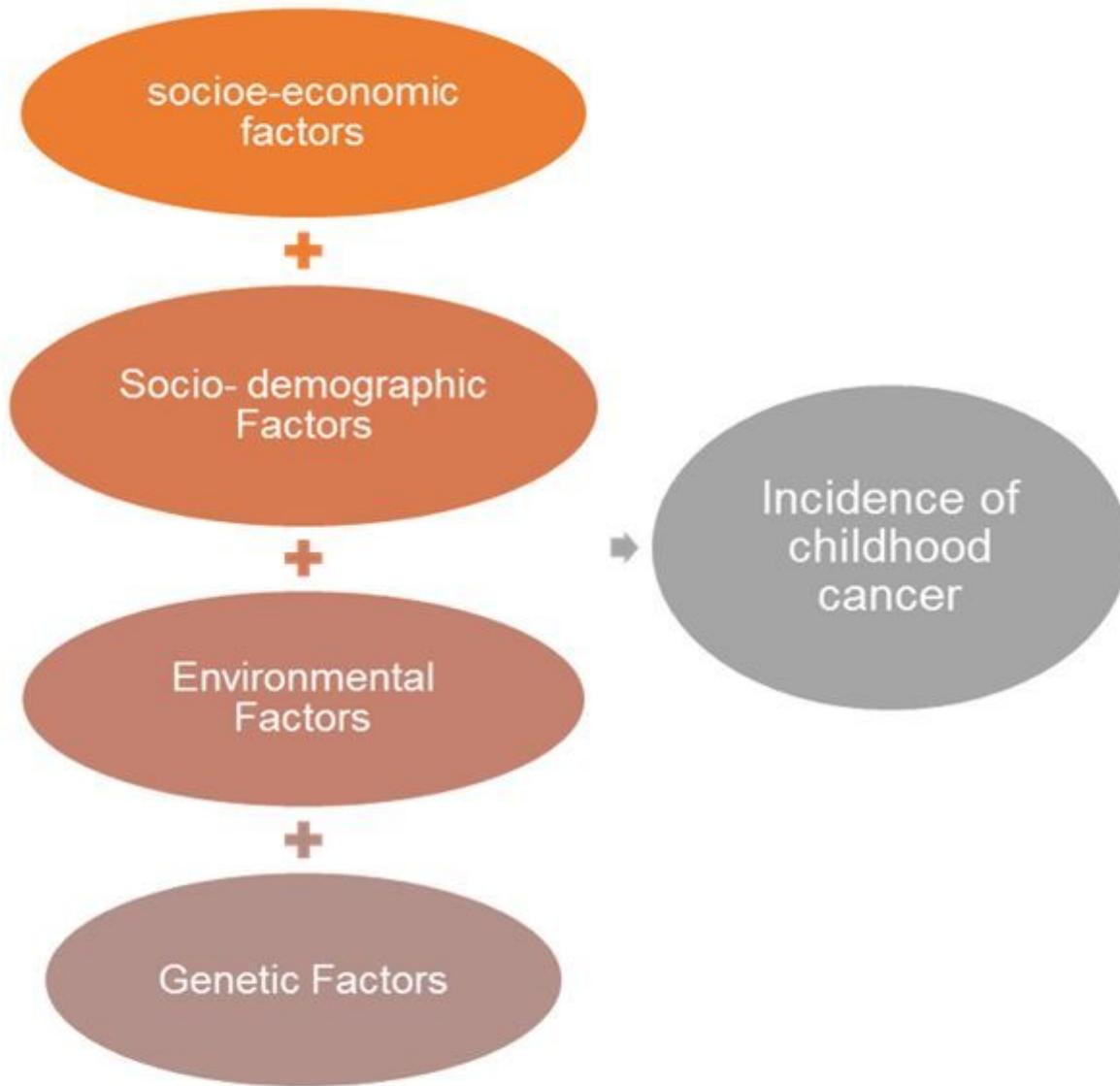
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## Figures



**Figure 1**

Conceptual framework of this study.