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Increased incidence of childhood leukemia in urban areas: a population-based case-control study

Il rischio di leucemia infantile è maggiore nella aree urbane: uno studio caso-controllo di popolazione

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Abstract

Objective. We carried out a population-based case-control study to assess the possibility of an excess risk of childhood leukemia in urban areas, independently from road traffic pollution.

Methods. Study subjects were the 111 cases of childhood leukemia diagnosed from 1998 to 2011 among residents of two provinces of the northern Italian Emilia-Romagna region, and 444 controls matched by age and sex. Through mapping of the region carried out by remote sensing, we examined the percentage of urban or rural area in the 100-meter circular buffer around each child's house. We also modeled annual average exposure to benzene and PM10 from vehicular traffic at each residence.

Results. In a multivariate model adjusting for benzene and PM10, the odds ratio of leukemia associated with residence in a highly urbanized area and residential area (≥95% land use of this type near the child's home) was 1.4 (95% confidence intervals 0.8-2.4) and 1.3 (0.8-2.2), respectively. An increased risk was also found in association with the proximity to «dumps, scrap yards, and building sites». No association emerged with residence in rural areas or near industrial plants.

Conclusions. These results indicate that children living in urban areas experience an excess leukemia risk, independently from exposure to pollutants from vehicles.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 102-107)
Key words: childhood leukemia, urban area, benzene, PM10

Riassunto

Obiettivo. Abbiamo condotto uno studio caso-controllo di popolazione per valutare la possibile associazione tra incidenza di leucemia infantile e residenza in aree urbanizzate, indipendentemente dall'esposizione a inquinanti da traffico autoveicolare.

Metodi. Abbiamo individuato i 111 casi di leucemia infantile diagnosticati nel periodo 1998-2011 nelle province di Modena e Reggio Emilia e una popolazione di controllo, costituita da quattro bambini appaiati per sesso, anno di nascita e provincia di residenza a ciascun caso. Di tali bambini abbiamo georeferenziato l'indirizzo di residenza e determinato l'uso del suolo nelle immediate vicinanze (100 m), basandoci sulla mappatura del territorio regionale effettuata mediante telerilevamento.

Risultati. Il rischio relativo di leucemia nei bambini residenti in aree urbane o più strettamente residenziali (uso del suolo di tali tipologie ≥95%) è risultato rispettivamente pari a 1.4 (intervalli di confidenza al 95%: 0.8-2.4) e 1.3 (0.8-2.2), dopo aggiustamento per benzene e PM10. Un incremento del rischio è risultato associato anche alla prossimità ad aree estrattive, discariche e cantieri, mentre nessuna associazione è emersa con la residenza in aree rurali o industrializzate.

Conclusioni. Questi risultati suggeriscono come la residenza in aree altamente urbanizzate sia associata a un incremento del rischio di leucemia infantile, indipendentemente dall'inquinamento autoveicolare.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 102-107)
Parole chiave: leucemia infantile, area urbana, benzene, PM10

BACKGROUND

Childhood cancer is a primary cause of death in children and adolescents in the industrialized world, the most common form (around 30%) being leukaemia. The causes of childhood leukaemia, unfortunately, still remain largely unknown.[1] About 5%-10% of childhood leukaemia is ascribed to ionizing radiation, congenital genetic anomalies,[2] and inherited conditions such as ataxia telangiectasia.[3] For the remaining cases, suspected risk factors are parental occupational exposures,[4] magnetic fields from high-voltage lines,[5] dietary factors,[6] exposure to chemicals (pesticides, paints, and household solvents),[7] and parental smoking.[8] Residential proximity to industries has been associated with an increased risk of childhood leukaemia.[9] An excess risk of childhood leukaemia has also been observed in urban areas of several countries in some[9-11] though not all studies,[12] and it has been ascribed to exposure to benzene and other traffic-related toxins,[13] or to the nearby presence of industrial plants and waste incinerators.[9] However, infectious agents spread through interpersonal contact, which is more likely in urban areas where population density is very high, might also be involved in the excess disease incidence seen in urban sites. Therefore, it has been proposed that infections and immunologic mechanisms may play a role in leukaemia aetiology, particularly for the acute lymphoblastic subtype, and this hypothesis is supported by some epidemiological features of the disease, such as age distribution, with its peak at 3-4 years, the greater incidence in developed countries, and a history of clustering.[14]

Leukaemia might be caused by an abnormal immune response to common infection during early life.[15,16] The existence of a specific leukaemia-causing agent, causing epidemic episodes in particular population mixing, has also been proposed.[17,18]

We carried out a case-control study in a northern Italian population to ascertain the possible effect of residence in urban areas on childhood leukaemia risk, taking into account exposure to traffic-related atmospheric pollutants.

METHODS

Study population

We identified all cases of childhood leukaemia newly diagnosed from 1998 to 2011 in children aged 0-14 while residing in Modena and Reggio Emilia, two provinces (total population about 1,200,000) of the Emilia-Romagna region in northern Italy.

Cases, along with their leukaemia subtype, were identified through the nation-wide hospital-based registry of childhood malignancies managed by the Associazione italiana ematologia oncologia pediatrica (AIEOP),[19] which also made it possible to retrieve the children's residence at diagnosis. For each case, we randomly selected four population controls among all residents with the same year of birth, sex, and province of residence, using the historical population databases of the National Health Service to match them by calendar year of case diagnosis, as well.

We also collected information about paternal annual income for the index year from the Revenue Agency of the Ministry of Finance database, as an indication of family socio-economic status.

Exposure assessment

We georeferenced the residential houses of patients at diagnosis and of the matched controls in the corresponding year in a Geographical Information System (GIS) using Arc-GIS software (version 9.2, ESRI, Redlands, CA 2006). The satellite coordinates of the residences were retrieved from a database available from the Modena and Reggio Emilia Provinces Service or, for addresses not included in the database, through Google Earth or a direct in loco measure using a portable GPS device (GPSmap 60CSx, Garmin Int. Corp., Olathe, KS).

We assessed the types of land use near each geocoded home according to GIS-based information collected by the Emilia-Romagna region by remote sensing in the year 2003 (the best one available for the study period). The Land Use Map 2003 for the Modena and Reggio Emilia provinces is available from the «Emilia-Romagna Geoportal»;[20] it contains a detailed description of land use with the specifications of Corine Land Cover.[21] Roads, including names, technical and administrative classification were also obtained from the cartographic archive of Emilia-Romagna region . We defined a circular buffer with a 100-meter radius around each child's home, and we selected for the study analysis two major predefined subtypes of land use: «urban area» and «rural area». «Urban area» included anthropic structured spaces and surfaces with residential buildings, roads, railways, production/commercial plants, public/private services, networks for water distribution and for production/transportation of energy. «Rural area» comprised territories allocated to agriculture with crop fields dedicated to different cultivations. «Urban area» was further detailed in three specific subtypes: «residential», «industrial plants», and «dumps, scrap yards, and building sites». «Residential» area refers to surfaces covered by over 50% by buildings intended for exclusive residential use. «Industrial plants» included industrial manufacturing facilities, factories, waste incinerators, water treatment plants, hospitals. «Dumps, scrap yards, and building sites» comprised the mining and quarrying of sand, gravel, stone, or other material, industrial scrap yards or repository, waste landfills, and construction sites. Finally, we calculated the percentages of rural and urban area, with their specific subcategories, within each circular buffer, using Python programming language, directly related to the GIS environment.

For patients diagnosed with leukaemia before 2010 and their controls, we also had the modeled exposure at the home of residence to benzene and particulate matter ≤10 μm (PM10) from motorized traffic available from a previous study.[22] Briefly, the CAlifornia LINE Source Dispersion Model, version 4 (CALINE4),[23] a line source air quality model, had been used to model the dispersion of emissions from vehicular traffic, considering specific vehicular emission factors for pollutants, vehicular traffic flow parameters for the main roads of both provinces and meteorological data. Such information could not be computed for the few subjects residing in sparsely populated mountain municipalities, for methodological reasons.[22]

Data analysis

We estimated the relative risk of childhood leukaemia associated with the intensity of urbanization by calculating the disease odds ratios (ORs) and their 95% confidence intervals (CI) in crude and multivariate conditional logistic regression models, according to percentage of land use within a 100-meter circular buffer around the child's home. The multivariate model was adjusted for exposure to benzene and PM10, two pollutants from vehicular traffic, and also for paternal income when available. The linearity of the associations between land use and disease risk was tested by computing a P value for trend based on percentage of area subtype as a continuous variable in the conditional logistic regression model. We also modeled the relationship between percentage of urbanized area and risk of leukaemia using restricted cubic splines, using the "mkspline" and "xblc" commands in Stata 13.[24] The optimal number of knots was selected using Akaike's information criterion (AIC), with knot placement as recommended by Harrell.[25] Based on the lowest AIC, we selected a model with three knots, placed at the 10th, 50th, and 90th percentiles.

RESULTS

We identified 111 newly-diagnosed cases of childhood leukaemia during the study period, including 86 (77.5%) of acute lymphoblastic subtype (ALL) (average age at diagnosis 6.1, standard deviation 3.8 years), 22 (19.8%) of acute myeloid subtype (AML) (5.3±4.9) and 3 cases included in the chronic myeloid category. Four hundred and forty four controls were also included in the study. Sixty five (58.5%) cases and 235 (52.9%) controls lived in highly-urbanized areas having ≥95% of «urban area» land use within the 100-meter circular buffer around the home building. Most of them were also living in areas defined as «residential» (38 [34.2%] cases and 133 [29.9%] controls), while a few of them lived in areas characterized as «industries» or «dumps, scrap yards, and building sites». Only four (3.6%) cases and 24 (5.4%) controls lived in areas defined as «rural», i.e., having ≥95% of «rural» land use. Benzene concentration was higher for children living in intensely urbanized districts (0.5 μg/m^3) than for those living in a «rural» area (0.1 μg/m^3), while concentrations of PM10 were substantially similar in both environments (6.6 and 6.5 μg/m^3, respectively).

Table 1 reports the OR of childhood leukaemia subtypes associated with a 10% increase in specific land uses within the 100-meter circular buffer around the child's home building. The urban area was further split into «residential» area, «industrial plants», and «dumps, scrap yards, and building sites». Adjusted analyses for annual average benzene and PM10 exposure showed an increased risk related to each 10% increase in residence in an «urban area» for all leukaemia (OR 1.05; 95%CI 0.95-1.16) and for single-disease subtype with an OR of 1.06 (0.95-1.19) and 1.02 (0.81-1.29) for ALL and AML, respectively. Analysis for specific subcategories of urban area showed an increased risk for «residential» areas (1.04; 0.97-1.12), no association with «industrial plants», and an excess incidence in relation with residence near «dumps, scrap yards, and building sites» (1.36; 0.75-2.49), especially for AML (11.15; 0.39-322.6). No association with «rural area» was identified.

Table 2 shows the OR of childhood leukaemia related to high intensity of urban or residential land use (≥95% around the child's home), according to child age and leukaemia subtype. The relative risk of leukaemia in children living in such a

	All leukemia (cases/controls 111/444)		ALL[1] (cases/controls 86/344)		AML[1] (cases/controls 22/88)	
	OR (95%CI)	P-trend[2]	OR (95%CI)	P-trend[2]	OR (95%CI)	P-trend[2]
urban area						
crude[3]	1.02 (0.94-1.10)	0.667	1.00 (0.92-1.09)	0.975	1.07 (0.88-1.31)	0.489
adjusted[4]	1.05 (0.95-1.16)	0.321	1.06 (0.95-1.19)	0.293	1.02 (0.81-1.29)	0.879
residential area						
crude[3]	1.03 (0.97-1.09)	0.350	1.03 (0.96-1.10)	0.441	1.05 (0.91-1.21)	0484
adjusted[4]	1.04 (0.97-1.12)	0.292	1.04 (0.96-1.14)	0.309	1.04 (0.88-1.24)	0.622
industrial plants						
crude[3]	1.01 (0.91-1.13)	0.826	1.01 (0.91-1.13)	0.826	1.03 (0.81-1.31)	0.787
adjusted[4]	0.99 (0.87-1.12)	0.876	1.02 (0.89-1.18)	0.744	0.93 (0.69-1.26)	0.643
dumps, scrap yards, building sites						
crude[3]	0.92 (0.60-1.39)	0.680	0.79 (0.45-1.38)	0.405	9.92 (0.35-279.6)	0.178
adjusted[4]	1.36 (0.75-2.49)	0.312	1.06 (0.51-2.22)	0.868	11.15 (0.39-322.6)	0.160
rural area						
crude[3]	0.96 (0.89-1.05)	0.382	0.98 (0.89-1.07)	0.581	0.94 (0.77-1.15)	0.534
adjusted[4]	0.94 (0.84-1.04)	0.218	0.92 (0.42-1.75)	0.181	0.99 (0.78-1.24)	0.909

[1]ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia
[2]P for linear trend based on continuous values
[3]crude analysis
[4]analysis adjusted for annual average atmospheric concentration (μg/m^3) of benzene and PM10; estimates not possible for subjects diagnosed after 2009 or residing in mountain municipalities

Table 1. Odds ratios (OR) with 95% confidence intervals (95%CI) of overall and subtype-specific childhood leukaemia associated with a 10% increase in specific land uses within the 100-meter circular buffer around the child's home building.
Tabella 1. Odds ratios (OR) e intervalli di confidenza al 95% (IC 95%) di leucemia infantile associati a incremento del 10% di differenti tipologie di uso del suolo presenti nell'area circolare di 100 metri di raggio definita intorno alla abitazione di ogni bambino.

	Urban area					Residential area				
	<95%[1]		≥95%			<95%[1]		≥95%		
	cases/ controls	OR	cases/ controls	OR (95%CI)	P-trend[2]	cases/ controls	OR	cases/ controls	OR (95%CI)	P-trend[2]
all leukemia										
crude	46/191	1.00	65/235	1.07 (0.69-1.66)	0.667	73/311	1.00	38/133	1.22 (0.78-1.89)	0.350
adjusted[3]	28/138	1.00	55/194	1.36 (0.78-2.37)	0.321	51/227	1.00	32/105	1.33 (0.81-2.20)	0.292
age <5 years										
crude	22/97	1.00	34/127	1.19 (0.64-2.21)	0.811	38/157	1.00	18/67	1.11 (0.59-2.07)	0.999
adjusted[3]	10/61	1.00	28/91	1.32 (0.54-3.24)	0.968	23/102	1.00	15/50	1.21 (0.57-2.59)	0.374
age ≥5 years										
crude	24/94	1.00	31/126	0.96 (0.52-1.79)	0.711	35/154	1.00	20/66	1.34 (0.72-2.49)	0.188
adjusted[3]	18/77	1.00	27/103	1.32 (0.54-3.24)	0.279	28/125	1.00	17/55	1.38 (0.69-2.76)	0.097
ALL										
crude	38/144	1.00	48/200	0.90 (0.55-1.48)	0.975	58/241	1.00	28/103	1.23 (0.69-2.19)	0.441
adjusted[3]	22/105	1.00	42/151	1.33 (0.70-2.49)	0.293	40/173	1.00	24/83	0.97 (0.49-1.92)	0.309
age <5 years										
crude	18/66	1.00	24/102	0.86 (0.42-1.72)	0.674	31/113	1.00	11/55	0.74 (0.35-1.56)	0.542
adjusted[3]	7/40	1.00	20/68	1.38 (0.49-3.87)	0.851	18/68	1.00	9/40	0.85 (0.35-2.09)	0.382
age ≥5 years										
crude	20/78	1.00	24/98	0.95 (0.47-1.92)	0.666	27/128	1.00	17/48	1.71 (0.84-3.49)	0.098
adjusted[3]	15/65	1.00	22/83	1.24 (0.54-2.81)	0.267	22/105	1.00	15/43	1.68 (0.77-3.67)	0.071
AML										
crude	7/42	1.00	15/46	2.03 (0.73-5.72)	0.489	12/61	1.00	10/27	1.87 (0.72-4.86)	0.484
adjusted[3]	5/33	1.00	13/39	1.96 (0.55-6.96)	0.879	10/51	1.00	8/21	1.71 (0.57-5.12)	0.622
age <5 years										
crude	3/28	1.00	9/20	5.00 (1.00-24.90)	0.315	5/38	1.00	7/10	7.04 (1.38-35.8)	0.225
adjusted[3]	2/21	1.00	8/19	2.05 (0.26-16.37)	0.692	4/31	1.00	6/9	4.12 (0.67-25.2)	0.966
age ≥5 years										
crude	4/14	1.00	6/26	0.81 (0.20-3.25)	0.749	7/23	1.00	3/17	0.61 (0.14-2.53)	0.775
adjusted[3]	3/12	1.00	5/20	1.25 (0.24-6.41)	0.970	6/20	1.00	2/12	0.65 (0.12-3.42)	0.979

[1]urban and residential use <95% used as reference category

[2]P for linear trend based on continuous values of land use

[3]adjusted for annual average atmospheric concentration (μg/m^3) of benzene and PM10; estimates not possible for subjects diagnosed after 2009 or residing in mountain municipalities

Table 2. Crude and adjusted odds ratios (OR) with 95% confidence intervals (95%CI) of childhood leukaemia in highly urbanized areas (≥95% of urban or residential use in the 100-meter circular buffer around the child's home building), according to age group and leukemia subtype (ALL, acute lymphoblastic leukaemia, and AML, acute myeloid leukaemia) .

Tabella 2. Odds ratios (OR) e intervalli di confidenza al 95% (95%CI) di leucemia infantile associati alla residenza in aree altamente urbanizzate (>95% di area residenziale nel buffer circolare di 100 metri di raggio definito intorno alla abitazione), per fasce di età e sottotipo di leucemia (ALL, leucemia linfatica acuta e AML, leucemia mieloide acuta).

highly urbanized area, after adjustment for atmospheric concentrations of benzene and PM10, was 1.36 (0.78-2.37). Considering only «residential» land use and investigating the two different subtypes of leukaemia, we found that the increased risk for ALL was confined exclusively to children ≥5 years, while for AML the opposite was true.

Spline regression analysis with adjustment for the matching variables, benzene and PM10 exposure also suggested a positive association between percentage of urbanized area and leukaemia risk (figure 1).

When we also adjusted the analysis for paternal income, the OR did not change (data not shown), but estimates were more unstable, as data were only available for 77% of the study subjects.

CONCLUSIONS

A greater incidence of childhood leukaemia in urban than rural areas has already been noted for several countries.[9] This increased risk was often attributed to high exposure to atmospheric benzene and other pollutants from motor vehicular traffic, or to the nearby presence of industrial plants, waste incinerators, or other sources releasing potentially carcinogenic chemicals.[9-11,13] Other authors suggested that the excess risk found in urban areas was due to the spread of infectious agents through interpersonal contact, which is clearly more intense in urban areas where population density is higher and the proportion of commuters or immigrant residents is higher, with an increased degree of population mixing,[26] though some evidence is inconsistent with this hypothesis.[27]

Findings of our study indicate that children living in highly urbanized areas have an increased risk of leukaemia compared to those living in rural areas, and that such excess risk is present regardless of exposure to benzene and PM10 from vehicular traffic, likely risk factors for this disease.[13,22] Our analysis also shows that childhood leukaemia risk is higher near «dumps, scrap yards, and building sites» or in areas generally defined as «residential».

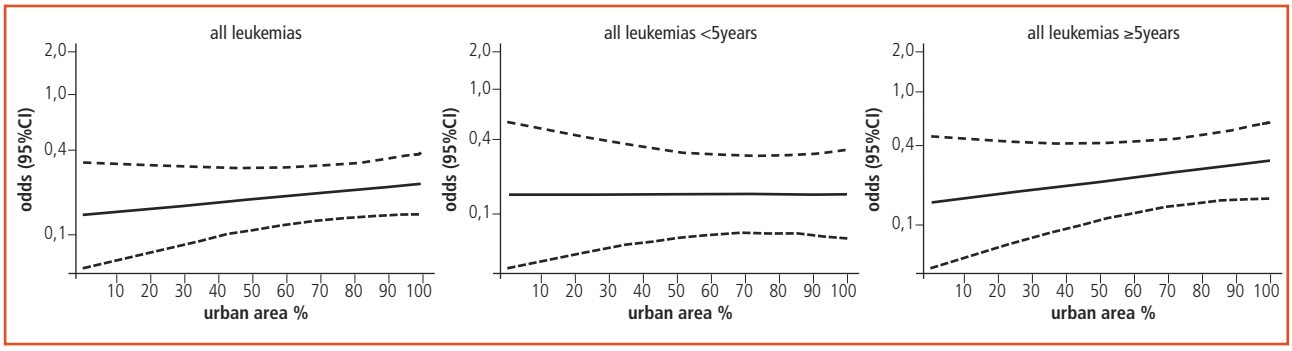

Figure 1. Natural cubic spline models from a generalized additive model for the relation between odds of case status and percentage of urban use controlling for benzene and PM10 exposure.
Figura 1. Rappresentazione grafica della relazione tra rischio di leucemia e uso del suolo presso l'abitazione di residenza.

Overall, these findings are consistent with the hypothesis of an infectious and immunological etiology of the disease, taking into account that our urban and particularly residential areas are characterized by the highest population density and strongly promote social interpersonal contacts. A role for infectious and immunologic mechanisms in the aetiology of childhood leukaemia, particularly of ALL, is supported by some epidemiological features of the disease, such as age distribution, with its peak at 3-4 years, greater incidence in developed countries, and history of clustering. It is possible that, particularly in genetically susceptible children, the immune system may suffer from lack of sufficient microbial challenges during early life due to extremely high hygienic conditions, thus developing an altered response to infections later encountered in childhood (the so-called «hygiene» or «delayed infection» hypothesis).[15,16,28] Alternatively, a specific leukaemia-causing agent may exist,[17] promoting the onset of the disease in densely-populated areas, and this might be due to viruses such as human herpesvirus and polyomavirus.[14]
The lower risk experienced in our study population by children living in rural areas might be hypothetically explained by adequate stimulation of the immune system in early life, as they are more subject to exposure to microbiological agents owing to their different lifestyle (more time spent outdoors, homes on the ground floor, windows open longer, larger families, more children per family) and less careful and sophisticated hygienic conditions compared with children living in cities and more generally in urban areas. In addition, this lower risk observed in rural areas does not appear to support a role of environmental pesticide exposure in leukaemia aetiology.
Of interest is the excess ALL risk that we found in children aged ≥5 years living in residential areas, after adjustment for vehicular traffic. This may support the hypothesis of a second mutation occurring at around 3-5 years of age, shortly before the occurrence of the typical peak of this specific leukaemia subtype.[16] We also saw an excess risk for AML <5 years, and this observation agrees with what has already been noted for this disease subtype, which showed a typical peak in the neonatal period and in adolescence.
The increased risk associated with residing near «dumps, scrap yards, and building sites» might be attributed to the presence of toxic substances in the nearby environment. However, lack of measured or modeled data on the amount and type of chemical pollution present in such study areas, including the possible release of benzene and PM10 from other sources than vehicular traffic, and the very low number of exposed children on which these statistically unstable risk estimates were based greatly hamper the evaluation of this finding.
In conclusion, our study indicates that an excess risk of childhood leukaemia exists in urban areas, particularly residential ones, and that such excess may not entirely be ascribed to pollution from motorized traffic. These results are consistent with the hypothesis of a role of infectious agents and insufficient stimulation of the immune system in early life in the etiology of childhood leukaemia.

Conflicts of interest: none declared

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