ARTICLE 7

Cancer incidence in children and young adults living in industrially contaminated sites: from the Italian experience to the development of an international surveillance system

Ivano Iavarone,[1] Carlotta Buzzoni,[2] Giorgia Stoppa,[2] Eva Steliarova-Foucher,[3] SENTIERI-AIRTUM Working Group*

[1] Department of Environment and Health, Italian Institute of Health (ISS), Rome (Italy)
[2] Clinical and Descriptive Epidemiology Unit, Oncological Network, Prevention, and Research Institute (ISPRO), Florence (Italy)
[3] Section of Cancer Surveillance, International Agency for Research on Cancer, World Health Organization, Lyon (France)
* see box (p. 84) for the list of the members of the working group

Corresponding author: Ivano Iavarone; ivano.iavarone@iss.it

ABSTRACT

BACKGROUND: this paper is based upon work from COST Action ICSHNet. Children's environmental health is on the 2030 Agenda for Sustainable Development. The incidence of childhood cancer is increasing worldwide and in Europe. Yet, the aetiology of most childhood cancers, including the role of environmental carcinogens, is still largely unknown. Contaminated areas, especially of industrial origin, are of high concern due to complex mix of hazardous pollutants and their potential health impacts on human populations, notably in children.

OBJECTIVES: to describe cancer risk in children and young adults (YA) residing in national priority contaminated sites (NPCSs) in Italy and to provide a suitable framework for a development of cancer surveillance in industrially contaminated sites (ICSs) in Europe.

METHODS: this study is based on a collaborative work of the Italian Institute of Health (ISS) and the Italian Association of Cancer Registries (AIRTUM), in the context of the SENTIERI project (Epidemiological study of residents in National Priority Contaminated Sites). Incidence rates were standardised according to the European standard population. The number of observed cases was compared to the expected cases derived from the age-, sex-, and cancer-specific incidence rates of the national pool of AIRTUM registries for the period 2006-2013. Standardized incidence ratios (SIRs) and 90% confidence intervals (CIs) were computed. The study reports the cancer profile in all combined 28 NPCSs covered by 22 cancer registries.

RESULTS: 1,050 cases of malignant tumours (MTs) were recorded among 3,161,786 person-years in people aged 0-29 years in 28 NPCSs (SIR: 1.03; 90%CI 0.98-1.09), with an age-standardised incidence rate of 317 per million. Excess risks were observed for: MT of the central nervous system in the age-group <1 year (SIR: 3.2; 90%CI 1.4-6.3); soft tissue sarcoma in the age-group 0-14 years (SIR: 1.6; 90%CI 1.1-2.3); acute myeloid leukaemia in the age-group 0-14 years (SIR: 1.7; 90%CI 1.1-2.4); non-Hodgkin lymphoma in the age-group 20-24 years (SIR 1.5; 90%CI 1.1-2.1), and germ cell tumours of male gonads in the age-group 20-29 years (SIR: 1.33; 90%CI 1.1-1.5). A deficit of cases was observed for Hodgkin lymphomas in the age-group 20-29 years (SIR 0.8; 90%CI 0.6-1.0).

DISCUSSION: this study, which is based on standardized methods and accredited information sources, supports the hypothesis that living in an NPCS increases the risk of some cancer types in children and young adults. Further work will concern groups of NPCSs characterised by common sources of contamination/key carcinogenic pollutants. In fact, in a novel project proposal we aim to monitor the cancer profile in children living in ICSs in Europe. The new project, based on the SENTIERI-AIRTUM methodology, will build on the networking activities of the COST Action on Industrially Contaminated Sites and Health Networking (ICSHNet) and childhood cancer studies coordinated by the International Agency for research on Cancer (IARC).

Keywords: child, young adult, cancer incidence, aetiology, contaminated sites, industry, surveillance

KEYPOINTS

What is already known

- **The overall cancer incidence for all tumours in children aged 0-14 years is increasing worldwide; this increase concerns also high-income Countries. Despite the documented high susceptibility of children to environmental pollutants, the overall evidence linking environmental carcinogens to the incidence of childhood cancer is mostly inadequate.**
- **Previous findings of the collaborative work of the Italian Institute of Health (ISS) and the Italian Association of Cancer Registries (AIRTUM), in the context of the SENTIERI project, showed an excess risk in the overall cancer incidence (9% in men and 7% in women), and in particular for several cancer sites in the residents exposed to the national priority contaminated sites (NPCSs).**

What this paper adds

- **This paper identifies, for the first time, possible increase in risk of cancer in children and young adults living in NPCSs and paves the way for further assessments and researches to verify specific aetiological hypothesis.**
- **A new international framework for the surveillance of cancer incidence in children and young adults living in industrially contaminated areas across Europe based on standardized methodologies and accredited information sources is outlined.**

INTRODUCTION

Cancer is a rare event in young age, with age-standardized annual incidence of 140.6 per million at age 0-14 years, and 185.3 per million in adolescents (15-19 years). Nonetheless, cancer is one of the leading causes of death in children, ranking after accidents, and the incidence of childhood cancers is increasing worldwide and both in low- and high-income regions, Europe included.[1]

The causes of childhood neoplasms are still largely unknown with about 5%-10% tumours which are genetically predisposed.[2-4]

Like in adults, most childhood cancers are thought to be activated by somatic gene mutations. In adults, this process is associated with aging and long-term exposure to carcinogens, while the rarity of childhood cancers and difficulties in evaluating the exposures of young children makes it difficult to establish a causal role of the environment.[5]

Several aspects contribute to making the evaluation of cancer risk in children a priority in relation to the exposure to environmental contaminants. As compared to adults, children have higher exposures to environmental agents due to unique activity patterns, behaviour and physiological characteristics, and immaturity of organs and systems.[6] Children spend more time outdoors, have higher respiratory rates, breathe larger volumes of air, and ingest proportionately more water and food than adults. They also play close to the ground in contact with dirt, which can include toxicants.[7,8]

Simultaneously, children are not significantly exposed to many lifestyle factors affecting adults nor experience direct occupational exposures, at least in most high-income Countries. Therefore, stronger effect and less confounders could be expected in childhood compared to adult population when investigating the role of environmental factors. However, in some low-income Countries children may be involved in hazardous works, like scavenging on landfill sites looking for electronic waste and, therefore, exposed to their toxic components (lead, mercury, cadmium), working in mining and smelting with exposure to asbestos, heavy metals and arsenic, and working in agriculture and exposed to pesticides.[9,10]

Another key distinction is the pattern of tumour types in children compared to adults. The most common cancers in children are leukaemia, tumours of the central nervous system (CNS), and embryonal tumours like neuroblastoma, hepatoblastoma, and retinoblastoma.[1] The spectrum of cancers in adults and young adults is distinct from that in younger and older populations; it is mostly represented by bone sarcomas, lymphomas, and germ cell tumours, while some carcinomas, especially of thyroid and female breast, start to be observed and become more frequent with age.[11,12]

The prenatal and early childhood periods represent a window of particular vulnerability, characterised by an increased risk of diseases including respiratory disorders, congenital anomalies, infections, and cancers.[8] The World Health Organisation (WHO) estimated that 26% (95%CI 16%-38%) of deaths in children under five years of age could be prevented through the reduction of environmental risks, such as air pollution, unsafe water, sanitation, and inadequate hygiene or chemicals.[6] As far as cancer risks are concerned, based on an expert survey,[10] it is estimated that 17% (95%CI 7%-42%) of all cancer disease burden in children under five years can be attributed to environmental causes, and this estimate does not include cancers provoked through environmental exposures in childhood, but manifesting only in later life.

The contaminated areas are of high concern from a public health perspective, due to the presence of mix of hazardous and carcinogenic contaminants with potential health impact on local populations including children. Past industrial activities have left a legacy of thousands of these areas across Europe. About 342,000 sites with contaminated soil require clean-up, corresponding, on average, to 5.7 estimated contaminated sites per 10,000 inhabitants. The principal sources of contamination in these sites are represented – directly or indirectly – by industrial activities, including industrial waste disposal and treatment.[13]

Low-income populations are usually found to live in areas with high pollution and poor-quality housing, near industrial and waste dumping sites; so, children living in poor areas seem to be more vulnerable to these exposures than children living in more affluent neighbourhoods because they may cumulate chronic diseases, less healthy diet, and additional exposures, which may give ground to synergistic effects.[14] Moreover, children living in adverse social circumstances also lack access to quality healthcare to counterbalance environmental threats and reduce their health consequences.[15]

The need for evaluating the health status of populations living in contaminated sites of high concern for remediation (National Priority Contaminated Sites, NPCSs) has been raised in Italy through the SENTIERI project (Epidemiological Study of Residents in National Priority Contaminated Sites). A description of the main characteristics of Italian NPCSs is available elsewhere.[16,17] SENTIERI is based on a multi-outcome epidemiological descriptive approach, analysing mortality data, hospital discharge records, congenital malformation, and cancer incidence at municipal level. SENTIERI is currently monitoring the health of people living in 45 NPCSs, in-

volving 319 municipalities with an overall population of approximately 5.9 million people, with a specific focus on children and young adults (16-18 years). NPCSs comprise a variable number of municipalities (from 1 to more than 50) with a residing population ranging from less than one thousand to more than a million of inhabitants. The study described in this paper is part of the SENTIERI project.

This paper aims at reporting, for the first time, cancer incidence in children, adolescents, and young adults residing in Italian NPCSs and outlines a framework for the development of an international surveillance system on childhood cancer in industrially contaminated sites across Europe, building on this Italian experience.

METHODS

The evaluation of cancer risk in children and young adults living in Italian NPCSs within the SENTIERI project is based on a collaborative work between the Italian Association of Cancer Registries (AIRTUM) and the Italian Institute of Health (ISS).[20-22] AIRTUM[23] records cancer incidence through population-based cancer registries, and its data are incorporated in *Cancer Incidence in Five Continents*[24] and *International Incidence of Childhood Cancer*,[25] published by the International Agency for Research in Cancer (IARC). Previous findings of this collaborative work showed an excess risk in the overall cancer incidence (9% in men and 7% in women), supporting a role of environmental exposure to carcinogenic contaminants in NPCSs.[20]

Data included in the analyses were extracted from the AIRTUM database (which the authors last accessed on January 2017). AIRTUM cancer registries participating in the study are currently active in 28 out of 45 NPCSs included in SENTIERI project: 20 registries cover all ages and 2 registries are specialized in childhood cancers (0-19 years). A total population of 2.2 million people is covered by the AIRTUM registries in the 28 NPCSs, which represents more than one third of the 5.9 million people living in the vicinity of the 45 identified NPCSs in Italy. The details of NPCSs and their coverage by cancer registries are provided in table 1.

These 28 NPCSs are mainly located close to industrial areas, either active or abandoned, in which the levels of contaminants in the environmental media (soil, sediments, and/or water) exceed permitted values. Most of the 28 NPCSs are characterised by the presence of chemical plants (71%), dumping sites of industrial or hazardous waste (61%), refineries and/or petrochemical plants (32%), electric power plants (18%), steel plants (14%), and other sources. Some NPCSs, such as those located in Taranto, Priolo, and Gela (Southern Italy) or in Porto Marghera and 'Laghi di Mantova' (Northern Italy), are close to complex industrial settings including several types of industrial facilities and other sources of contamination (table 1). In all NPCSs included in the study, the contamination process precedes the beginning of this study.

The registered cancer cases were classified according to the Third Edition of the International Classification of Childhood Cancer (ICCC-3).[26] Given the scarce available evidence supporting a role of environmental factors in the aetiopathogenesis of childhood tumours, the rarity of these neoplasms, and the exploratory nature of the study, the analyses focused mainly on the most represented cancer types among children and adolescents. Thus, the analyses were conducted for the overall group of malignant tumours, the neoplasms of the lymphohaematopoietic tissue (including the main subgroups of leukaemias and lymphomas), and the tumours of the CNS. All malignant tumours and tumours of the CNS were analysed with and without the inclusion of benign tumours of the CNS.

In addition to the above-mentioned main diagnostic groups, this study also included neuroblastoma (the top-ranking malignancy in infants and counting for about 8% of malignancies in age 0-14), soft tissue sarcomas (around 6%-7% in paediatric and adolescent cases), and thyroid carcinomas (11% among adolescents). The class of germ cell, trophoblastic, and gonadal tumours was also included, as these neoplasms are frequent in the first year of life (about three times higher than in class 0-14) and represent 10% of neoplasms in adolescents, particularly when they are mainly located in the gonads (81%), specifically testis.[27]

Overall, the diagnostic groups selected for the analyses were expected to account for more than 75% of all malignancies recorded by AIRTUM registries among children and adolescents.[27]

Besides the above cancer types, for explorative purposes, this study also addressed the overlapping large category of embryonal tumours (as defined in table 2) and thyroid carcinomas, commonly observed in young adults.

This study assessed cancer incidence in all covered NPCSs combined. The number of expected figures for all malignant tumours and for each diagnostic group selected for the study was calculated for 7 age groups (<1 year, 1-4, 5-9, 10-14, 15-19, 20-24, and 25-29 years) and gender, based on cancer specific rates of the national pool of AIRTUM cancer registries in the period 2006-2013. The expected number of cases for each NPCS was based on the reference rates excluding the population at risk and cancer cases of the specific NPCS, so as to avoid dilution of the effect. The observed cases in all combined 28 NPCSs

NPCSs	REGISTRIES	YEARS AVAILABLE FROM THE REGISTRY FOR THE STUDY PERIOD	TOTAL PERSON-YEARS COVERED BY THE REGISTRY IN THE STUDY PERIOD AGE-GROUP: 0-29 YEARS	PERSON-YEARS OF NPCS-EXPOSED PEOPLE COVERED BY THE REGISTRY IN THE STUDY PERIOD*		MAIN SOURCES OF CONTAMINATION IN THE NPCSs**							
			No.	No.	%	A	AP	C	D	E	M	PR	S
Area industriale Basento	Basilicata	2006-2010	942,712	64,644	6,86	+		+					
Aree industriali Torres	Sassari	2006-2011	841,105	253,777	30,17		+	+	+	+		+	
Bacino Chienti	Marche^	2006-2007	533,277	20,161	3,78			+					
Balangero	Piemonte^	2006-2011	4,399,388	6,452	0,15	+			+		+		
Biancavilla	Catania-Messina-Enna	2006-2012	4,508,002	64,330	1,43	+					+		
Bolzano	Alto Adige	2006-2010	835,825	139,596	16,70			+					
Brescia Caffaro	Brescia	2006-2008	1,006,628	164,152	16,31			+	+				
Brindisi	Brindisi	2006-2008	406,028	89,061	21,93		+	+	+	+		+	
Broni	Pavia	2006-2009	537,934	8,412	1,56	+							
Casale Monferrato	Piemonte (Biella and Vercelli)	2006-2011	4,811,377	13,998	0,29	+							
Cengio Saliceto	Piemonte^	2006-2011	4,399,388	13,280	0,30			+	+				
Cerro Lambro	Milano	2007-2010	3,260,946	11,006	0,34				+				
Cogoleto Stoppani	Genova	2006-2009	809,893	19,759	2,44			+	+				
Falconara	Marche^	2006-2007	533,277	9,038	1,69			+		+		+	
Fidenza	Parma	2006-2013	896,687	94,629	10,55			+	+				
Gela	Ragusa-Caltanissetta	2007-2012	1,309,012	173,941	13,29			+	+			+	
Laghi Mantova	Mantova	2006-2010	552,307	73,536	13,31		+	+	+			+	
Milazzo	Catania- Messina-Enna	2006-2012	4,508,002	99,599	2,21					+		+	+
Pieve Vergonte	Piemonte^	2006-2011	4,399,388	5,592	0,13			+	+				
Pioltello Rodano	Milano	2007-2010	3,260,946	48,228	1,48			+	+				
Porto Marghera	Veneto	2006-2009	2,618,246	247,039	9,44		+	+	+	+		+	
Priolo	Siracusa	2006-2012	931,282	408,491	43,86	+	+	+	+			+	
Sassuolo Scandiano	Modena e Reggio Emilia	2006-2012	2,377,823	245,393	10,32			+					
Serravalle Scrivia	Piemonte^	2006-2011	4,399,388	8,264	0,19			+					
Taranto	Taranto	2006-2012	1,353,566	480,611	35,51		+		+			+	+
Terni	Umbria	2006-2013	1,933,755	222,011	11,48				+				+
Tito	Basilicata	2006-2010	942,712	12,004	1,27	+		+	+				+
Trento Nord	Trento	2006-2010	789,694	164,782	20,87			+					
Total person-years			**31,256,099**	**3,161,786**	**10,12**								

* of the total in the age-class 0-29 years.
** **A:** asbestos; **AP:** harbour area; **C:** chemical plant (production); **D:** landfill; **E:** electric power plant; **M:** mine and/or quarry; **PR:** petrochemical plant and/or refineries; **S:** steel plant.
^ specialised in childhood cancer registration (0-19 years).

Table 1. The overview of data available for the Children SENTIERI-AIRTUM study. National priority contaminated sites (NPCSs), cancer registries, study period, person-years, and main contamination sources. Study period 2006-2013.

AGE (YEARS)	ALL MALIGNANT TUMOURS		MALIGNANT TUMOURS, INCLUDING BENIGN CNS TUMOURS	
	OBS	SIR (90%CI)	OBS	SIR (90%CI)
≤1	30	1.26 (0.90-1.70)	32	1.26 (0.92-1.69)
0-4	76	0.99 (0.81-1.20)	81	0.98 (0.81-1.18)
5-9	62	0.99 (0.79-1.23)	71	1.01 (0.82-1.24)
10-14	86	1.15 (0.96-1.38)	92	1.11 (0.92-1.32)
15-19	139	1.00 (0.87-1.15)	146	0.99 (0.86-1.14)
20-24	273	1.16 (1.05-1.28)	285	1.17 (1.06-1.30)
25-29	384	0.95 (0.87-1.04)	397	0.96 (0.88-1.04)
20-29	657	1.03 (0.96-1.10)	682	1.04 (0.97-1.11)
0-14	254	1.07 (0.96-1.19)	276	1.06 (0.96-1.17)
0-19	393	1.04 (0.96-1.14)	422	1.03 (0.95-1.12)
0-24	666	1.09 (1.02-1.16)	707	1.09 (1.02-1.16)
0-29	1050	1.03 (0.98-1.09)	1104	1.04 (0.99-1.09)

Obs: number of observed incident cases **SIR:** standardized incidence ratio
90%CI: 90% confidence interval

Table 2. Cancer incidence in the 28 NPCSs for all malignant tumours as compared to the reference national pool of cancer registries (both genders by age class) (reference: AIRTUM 2013);[27] with and without benign CNS tumours (excluding embryonal cancers).

DIAGNOSTIC GROUP	ICCC-3 CODE*	OBSERVED CASES	
		No.	%
All malignant tumours*	I-XII	1,050	100
Lymphohaematopoietic tissue	I-II	331	32
• Leukaemia	I	142	14
Lymphoid leukemias	Ia	79	8
Acute myeloid leukemias	Ib	4	4
• Lymphoma	II	189	18
Hodgkin lymphomas	IIa	103	10
Non-Hodgkin lymphomas	IIb-c	71	7
Malignant tumours of central nervous system**	III	71	7
Neuroblastoma and other peripheral nervous-cell tumours	IV	19	2
Soft tissue and other extraosseous sarcomas	IX	47	4
Germ-cell and trophoblastic tumour, and neoplasms of the gonads	X	160	15
Thyroid carcinomas	XIb	137	13
Embryonal tumours***	IIIa; IIIc; IIIe; IVa; IVb; V; VIa; VIIa; VIIIc; IXa; IXd; Xa, Xb, Xc	242	23

* Steliarova-Foucher 2005.[25]
** The 54 benign CNS tumours are not included in the number of cases
*** Group of codes defined as in AIRTUM 2013[27] p.166; embryonal tumours are included also in some of the diagnostic groups listed above.

Table 3. Numbers of malignant cancer cases observed in the Children SENTIERI-AIRTUM study, by diagnostic group.

were then compared with the sum of expected cases in each NPCS calculated as above.
Standardized incidence ratios (SIRs) and 90% confidence intervals (CIs) were computed. The choice of the 90% significance level in SENTIERI was made to minimize the acritical use of CI as surrogate of hypothesis testing; such use could lead to consider as relevant only the estimators for which the CI exclude the null value, i.e., the ones customarily defined as "statistically significant". The discriminating use of statistical significance in the evaluation of causal associations in epidemiology has been discussed since 1965 and recently re-proposed as discussed by Comba and colleagues in 2014.[20] When studying the risk from rare diseases in vulnerable subgroups, like cancers in children, it is more important to avoid a potential excess risk than to demonstrate a lack of risk. In SENTIERI, the priority is to detect excesses or defects, represented, for example, by the direction of the risk estimators, while their size and precision can be fine-tuned, from a research perspective, in studies testing specific aetiological hypotheses, where the standard 95%CI are used.
Age-standardized incidence rates were calculated as weighted average of the age-specific rates for the following age groups: <1 year, 1-4 years, 5-9 years, 10-14 years, using the weights for the respective age groups of European (Scandinavian 1960) standard population.[28]

RESULTS

Overall, 1,050 new cases of malignant tumours (in the age group 0-29 years) among 3,161,786 person-years were recorded in 28 Italian NPCSs (involving 138 municipalities and 2.2 million people reported by the 2011 Census), with an average annual age-standardised incidence rate of 317 per million. The age-standardised rate was 172 per million in children (0-14 years), and the age-specific rates were 263 for adolescents (15-19 years), and 572 for young adults (20-29 years).
Out of 1,050 neoplasms observed in the broad age group (0-29 years): • 24.2% (254 cases) occurred in children (age 0-14 years), including 30 neoplasms (3%) in the first year of life; • 13.2% (139 cases) were detected in adolescents (age 15-19 years); • 62.6% (657 cases) among young adults (age 20-29 years) (table 2).
Overall, a 3% increase in cancer incidence for all malignant tumours was observed in all 28 combined NPCSs, for all ages (0-29 years), as compared to the reference background rates. This excess pertained in particular to the age class 0-24 years (SIR: 1.09; 90%CI 1.02-1.16; 666 cases), and to the young adults aged 20-24 years (SIR: 1.16; 90%CI 1.05-1.28; 273 cases). The inclusion of non-malignant CNS neoplasms (54 cases overall in the

AGE GROUP (YEARS)	LYMPHO-HAEMATOPOIETIC TISSUE		MALIGNANT TUMOURS OF CNS		MALIGNANT AND NON-MALIGNANT TUMOURS OF CNS		NEUROBLASTOMA		SOFT TISSUE AND OTHER EXTRA OSSEOUS SARCOMAS		THYROID CARCINOMAS	
	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)
≤1	5	1.22 (0.48-2.56)	6	3.19 (1.39-6.29)	8	2.38 (1.18-4.29)	6	0.70 (0.30-1.37)	< 3	1.67 (0.30-5.26)	0	0.00 (0.00-0.00)
0-14	131	1.12 (0.96-1.29)	37	1.18 (0.88-1.55)	59	1.08 (0.86-1.34)	18	0.87 (0.56-1.29)	21	1.62 (1.29-2.33)	< 3	0.39 (0.07-1.23)
15-19	57	0.92 (0.73-1.15)	10	1.13 (0.61-1.91)	17	0.98 (0.62-1.47)	< 3	5.61 (0.29-26.61)	7	0.88 (0.41-1.65)	17	0.95 (0.60-1.42)
20-29	143	0.90 (0.78-1.03)	24	0.99 (0.68-1.39)	49	1.18 (0.91-1.49)	0	0.00 –	19	0.84 (0.55-1.24)	118	1.07 (0.91-1.25)
0-19	188	1.05 (0.93-1.19)	47	1.17 (0.90-1.49)	76	1.06 (0.86-1.28)	19	0.91 (0.60-1.34)	28	1.34 (0.95-1.83)	19	0.82 (0.54-1.21)
0-29	331	0.98 (0.89-1.07)	71	1.10 (0.89-1.34)	125	1.10 (0.94-1.28)	19	0.88 (0.58-1.29)	47	1.08 (0.84-1.38)	137	1.03 (0.8-1.18)

Obs: number of observed incident cases **SIR:** standardized incidence ratio **90%CI:** 90% confidence interval

Table 4. Cancer incidence in the 28 NPCSs for the main diagnostic groups included in the analysis as compared to the reference national pool of cancer registries (both genders, by age group). Reference: AIRTUM 2013.[27]

AGE GROUP (YEARS)	ALL LEUKAEMIAS		LYMPHOID LEUKAEMIAS		ACUTE MYELOID LEUKAEMIAS		ALL LYMPHOMAS		HODGKIN LYMPHOMAS		NON-HODGKIN LYMPHOMAS	
	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)
≤1	5	1.39 (0.55-2.93)	< 3	1.35 (0.24-4.25)	<3	1.75 (0.31-5.52)	0	0.00 (0.00-0.00)	0	0.00 (0.00-0.00)	0	0.00 (0.00-0.00)
0-14	89	1.10 (0.92-1.32)	61	1.01 (0.81-1.25)	22	1.66 (1.12-2.37)	42	1.16 (0.88-1.50)	14	0.96 (0.58-1.51)	20	1.13 (0.75-1.64)
15-19	18	1.05 (0.68-1.55)	9	1.01 (0.53-1.76)	5	1.14 (0.45-2.39)	39	0.87 (0.65-1.14)	28	0.84 (0.60-1.15)	11	1.06 (0.60-1.76)
20-29	35	0.93 (0.68-1.23)	9	1.07 (0.56-1.86)	15	1.44 (0.89-2.21)	108	0.89 (0.75-1.04)	61	0.78 (0.62-0.96)	40	1.07 (0.80-1.39)
0-19	107	1.09 (0.93-1.28)	70	1.01 (0.82-1.23)	27	1.53 (1.08-2.11)	81	1.00 (0.82-1.20)	42	0.88 (0.67-1.14)	31	1.11 (0.80-1.49)
0-29	142	1.05 (0.91-1.20)	79	1.01 (0.83-1.22)	42	1.50 (1.14-1.93)	189	0.93 (0.82-1.05)	103	0.82 (0.69-0.96)	71	1.08 (0.88-1.32)

Obs: number of observed incident cases **SIR:** standardized incidence ratio **90%CI:** 90% confidence interval

Table 5. Cancer incidence in the 28 NPCSs for the diagnostic subgroups of lymphohaematopoietic tissues as compared to the reference national pool of cancer registries (both genders by age class). Reference: AIRTUM 2013.[27]

AGE (YEARS)	OVERALL				MALES				FEMALES			
	GERM-CELL AND TROPHOBLASTIC TUMOURS, AND NEOPLASMS OF THE GONADS		EMBRYONAL TUMOURS		GERM-CELL AND TROPHOBLASTIC TUMOURS, AND NEOPLASMS OF THE GONADS		EMBRYONAL TUMOURS		GERM-CELL AND TROPHOBLASTIC TUMOURS, AND NEOPLASMS OF THE GONADS		EMBRYONAL TUMOURS	
	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)	OBS	SIR (90%CI)
≤1	<3	0.76 (0.04-3.62)	22	1.30 (0.88-1.85)	<3	1.34 (0.07-6.37)	14	1.47 (0.89-2.30)	0	0.00 (0.00-0.00)	8	1.08 (0.54-1.94)
0-14	5	0.76 (0.30-1.60)	74	0.98 (0.80-1.19)	4	1.50 (0.51-3.44)	44	1.11 (0.85-1.43)	<3	0.26 (0.01-1.21)	30	0.84 (0.60-1.14)
15-19	11	0.84 (0.47-1.40)	20	0.83 (0.55-1.20)	8	0.76 (0.38-1.37)	15	0.86 (0.53-1.32)	3	1.20 (0.33-3.10)	5	0.76 (0.30-1.59)
20-29	144	1.34 (1.16-1.53)	148	1.26 (1.09-1.44)	129	1.33 (1.14-1.54)	136	1.33 (1.15-1.54)	15	1.38 (0.85-2.13)	12	0.78 (0.45-1.26)

Obs: number of observed incident cases **SIR:** standardized incidence ratio **90%CI:** 90% confidence interval

Table 6. Cancer incidence in the 28 NPCSs for the diagnostic groups of germ cell, trophoblastic tumours, and neoplasms of the gonads, and embryonal tumours as compared to the reference national pool of cancer registries (by gender and age class). Reference: AIRTUM 2013.[27]

8-year period) did not modify noticeably the SIRs or their CIs in any age group (table 2).

The diagnostic groups selected for the study accounted overall for 73% of all malignant tumours recorded in the 28 NPCSs, ranging from neuroblastomas (2%) to neoplasms of the lymphohaematopoietic tissue (32%). The category of embryonal tumours, as defined in this study, represented 23% of the total observed number of the malignant neoplasms (table 3), and 73% of cases in the first year of life (20 out of 30 tumours).

The analysis by diagnostic group (table 4) revealed excess risks for malignant tumours of CNS in the first year of life, and for soft tissue sarcomas among children aged 0-14 years. The observed numbers of neuroblastoma and thyroid cancer did not differ from the expected in any age group or by gender (data not shown). No risk excess

was observed for all combined lymphohaematopoietic tumours, although the SIR value suggested a possible 12% excess in children aged 0-14 years (within the 90%CI). Among subgroups of the lymphohaematopoietic malignancies (table 5), excesses were observed for acute myeloid leukaemias (AMLs) both in the age group 0-14 years (SIR: 1.66; 90%CI 1.12-2.37) and in the age group 0-29 years (SIR: 1.50; 90%CI 1.14-1.93), and for non-Hodgkin lymphomas among the subgroup of young adults aged 20-24 years (22 cases; SIR: 1.50; 90%CI 1.02-2.14; data not shown). A deficit of Hodgkin lymphomas was observed among young adults (20-29 years: SIR: 0.78; 90%CI 0.62-0.96) and in the overall 0-29 age group (SIR: 0.82; 90%CI 0.69-0.96).

A majority of cases classified to the composite diagnostic group of germ cell tumours, trophoblastic tumours, and neoplasms of the gonads occurred among male young adult aged 20-29 years (89% of cases) and had a 33% excess risk (129 cases; SIR: 1.33; 90%CI 1.14-1.54) (table 6).

The analysis restricted to malignant gonadal germ cell tumours (ICCC-3 code: Xc) highlighted that the above excess was entirely linked to testicular tumours (119 cases; SIR: 1.36; 90%CI 1.16-1.58; data not shown).

A very similar pattern of risk was detected for the embryonal tumours, with a 26% excess risk (148 cases; SIR: 1.26; 90%CI 1.09-1.44), related to males (136 cases; SIR: 1.33; 90%CI 1.15-1.54), confirming the excess risk impacting the testicular tumours.

DISCUSSION

This SENTIERI-AIRTUM study is, to the knowledge of the Authors, the first one describing cancer risk in children, adolescents, and young adults living in NPCSs in the frame of an epidemiological surveillance project with a standardised methodology.

This study concerned 28 NPCSs covered by AIRTUM cancer registries, involving 138 municipalities and 2.2 million people which represents around 37% of people living in all 45 NPCSs monitored by the SENTIERI project, involving 319 municipalities and approximately 5.9 million people. The coverage of cancer registration is rapidly increasing, with about 70% of Italian population covered by 49 accredited AIRTUM cancer registries, according to the AIRTUM database, which the Authors accessed in July 2018. Including the new areas in SENTIERI project can be, thus, envisaged and will increase the level of surveillance of the exposed populations.

Overall, 1,050 cases of malignant tumours were recorded among 3,161,786 person-years related to people aged 0-29 years living in 28 Italian NPCSs with a standardised incidence rate of 317 per million.

The results, significant on 10% level, point to some vulnerability of the childhood population to the exposures from NPCSs. Malignant tumours (all diagnostic groups combined) were in excess in the age class 0-24 years, in particular, among young adults aged 20-24 years. Concerning the lymphohaematopoietic tissue, excess risks were observed in relation to acute myeloid leukaemia both overall (0-29 years) and among children aged 0-14 years; an excess risk of non-Hodgkin lymphomas was detected among young adults (20-24 years). Other excesses concerned CNS tumours in the first year of life and soft tissue sarcomas in children (0-14 years), whose incidence was 60% higher than expected.

A 36% excess of testicular (germ-cell) tumours was observed in young adults (20-29 years). This also resulted in an excess risk of the embryonal tumours to which most testicular tumours are classified. The main reason to include this complex diagnostic group was their specific occurrence in children, especially among infants, and the fact that they share features and biology.[27] The causes of testicular germ-cell tumours have not been elucidated, but the incidence patterns suggest that a combination of genetic and environment factors are involved, with environmental factors predominating early in life.[29]

The strengths of the present study are the common standardized analytical method and accredited health information sources adopted across all NPCSs. The quality indicators of AIRTUM registries complies with the international standards.[24,25] In addition, internal accreditation procedure is in place within AIRTUM and validation procedures are routinely performed in the common database using software developed by AIRTUM (Check-AIRTUM).[23]

The results of the analyses on cancer profiles of children and young adults in relation to a single NPCS are the object of a further publication. On-going analyses are addressing the possibility to group NPCSs on the basis of similar industrial contamination sources. A planned characterization of the industrially contaminated sites in terms of key carcinogenic contaminants will also allow formulation of aetiological hypotheses to be evaluated in ad-hoc epidemiological studies.

Major limitations of this investigation are the lack of a quantitative indicator of exposure and the use of municipality as the smallest level of data aggregation, which undoubtedly dilutes the strength of effect. Due to the ecological design of the study, misclassification of exposure on individual level could not be ruled out. Further, risk estimates are not adjusted for potential confounders, which is most often the case in ecological studies. Confounders may play a role especially in young adults, who might be exposed to occupational and life-style risk factors.

In the present paper, the overall estimates were not ad-

justed for socioeconomic status (SES), as the appropriateness of adopting currently available SES indicators in Italy to adjust for deprivation in small-area environmental health studies is debated;[30] however, populations living in NPCS have a low SES.[31]

Some – though very few – epidemiological studies have specifically analysed cancer risks in children living in the proximity of industrial sites or in relation to exposure to contaminants emitted by industry or transportation, providing some support to a possible aetiological role or co-role of residential exposures to industrial emissions in the risk of childhood cancer.

Previous findings from a case-control study carried out in California[32] based on the Air Pollution and Childhood Cancer Study (APCC) showed an excess risk for germ-cell tumours and for acute myeloid leukaemia in relation to exposure to industrial emissions of dichloromethane in children aged 0-6 years. The risk of these cancer types was also elevated in the present study.

Another recent study estimated risk of cancer in children younger than <15 years resident in small geographical areas (census tracts) neighbouring air-polluting industries in the Murcia region in Spain.[33] The sources of pollution included energy industries, organic and inorganic chemical industries, pharmaceutical industries, building material industries, and industries related to incineration or valorisation of dangerous waste. An incidence value higher than expected of non-Hodgkin lymphomas were observed around (4 km) to all kind of industry in the study; sympathetic nervous system tumours (SNSTs) were in excess in people residing around energy and electric plants and organic and inorganic chemical industries group.

The risk of several cancer types has been analysed in children (0-14 years) in a series of population-based case-control studies (period 1996-2011) in relation to residential proximity to different industrial settings in Spain.[34-37] Risk of bone tumours[34] and renal tumours[35] was associated to residing close to any industrial facilities and close to specific industrial activities producing and processing of metals, to hazardous waste, and to combustion installations.

Childhood leukaemia[36] was in excess in children living near industries in general, and in particular those involved in production of glass and mineral fibres, surface treatment using organic solvents, galvanization, production and processing of metals, and surface treatment of metals. In another set of analyses concerning childhood rare tumours,[37] an association was observed for retinoblastoma and residence near industries in the sector of glass and mineral fibres and organic chemical industries.

Among the same series of studies, a further investigation showed that living in the intersection of industrial and urban areas may increase risk of CNS tumours, while living either in urban areas or in industrial areas did not seem to increase this risk. Moreover, the study highlights that children living in the most affluent areas had a 37% higher risk of developing CNS tumours than children living in most deprived areas.[38] The latter observation is in line with previous evidence linking the risk of developing CNS tumours with higher socioeconomic in the European Union.[39]

The results available from the above-mentioned studies support the need of assessments of cancer risk in relation to contamination from specific industrial activities, possibly looking at pollutants of specific carcinogenic effect.

The current available evidence linking childhood cancer to exposure to environmental carcinogens is largely inadequate for many chemicals that have been classified as carcinogenic in adults.[4] The main limitations of the environmental studies of cancer in children are generally associated with inadequate study design, scarce availability of exposure and outcome data, and the small fraction of children exposed to environmental carcinogens in common residential settings. These aspects imply a generally low statistical power to detect significantly increased risks.[18]

Focusing on communities living in industrially contaminated areas, with documented presence of high level of carcinogens (often in form of mixtures), may allow increasing the portion of the exposed populations, empowering the ability to detect excess risks of cancers in children residing in these areas.

This is the main hypothesis of a novel project proposal based on a collaborative agreement between ISS and the International Agency on Research on Cancer (IARC) aiming to assess the cancer risk profile in children and young people living in industrially contaminated sites (ICSs) across Europe.[22] The possibility to augment the size of the study population in ICSs will therefore also increase the power to identify thus far undetected associations.

The long-term goal of this new project is to establish and consolidate an international cancer surveillance system in these areas in order to monitor changes in the cancer profile and support the implementation (or the effectiveness) of remediation activities. Moreover, this project will also allow exploration of research hypotheses for populations residing close to specific industrial sources (i.e., petrochemical plants, refineries, chemical plants, steel plants, or industrial waste disposals) with an a-priori evidence of association with cancer risks in adults. The development of this surveillance system will be based on the SENTIERI-AIRTUM approach and will build on the networking activities of the COST Action ICSHNet,[40]

launched in 2015 to promote international coordination to deal with the environmental health challenges posed by ICSs. The Action currently involves 33 Countries; one of its main objectives is to protect children's health.
Cancer registries in many of the 33 Countries participating in the COST Action are also members of the International Association of Cancer Registries (IACR), which currently counts 164 cancer registries in Europe.[41] In 2014, it was estimated that at least 80% of population aged 0-14 years and more than 50% of population aged more than 15 years within the EU was covered by cancer registries, while lower proportions concern other European areas.[42] Many population-based cancer registries operating in Europe participate in international quality-assured studies, such as Cancer Incidence in Five Continents,[24] International Incidence of Childhood Cancer,[25] and Automated Childhood Cancer Information System,[43,44] and they are able to provide incidence data over the periods ranging from a few years to more than six decades on almost all tumour types.

CONCLUSIONS

The incidence of cancer in children and adolescents is increasing worldwide and both in low- and high-income regions, including Europe.[1,44] Despite the documented high susceptibility of children to environmental pollutants, the evidence linking the childhood cancer to environmental carcinogens is mostly inadequate.
This study provides indications that living in contaminated sites may increase risk of some cancer types in children (CNS, lymphohaematopoietic, sarcomas) and young adults (testicular germ-cell tumours). Ad hoc analytical studies are needed to verify specific aetiological hypotheses. Building on the SENTIERI-AIRTUM methodology, surveillance of cancer incidence in children and young adults living in industrially contaminated areas planned on European level will strengthen the evidence needed for implementation of potential preventive measures.

Conflict of interest disclosure: the authors declare they have no conflict of interest.

Acknowledgments: a particular thank goes to the Directors and staffs of the 22 AIRTUM Cancer Registries involved in the study.

Grant: this study is based on a collaborative work of the Italian Institute of Health (ISS) and the Italian Association of Cancer Registries (AIRTUM), in the context of the SENTIERI Project, 'Azione Centrale 2015' funded by the Italian Ministry of Health. The publication of this work was encouraged and supported by the COST Action IS1408 (ICSHNet).

SENTIERI-AIRTUM Working Group

Antonino Ardizzone (Registro tumori Brindisi)
Alessandro Barchielli (Registro tumori Toscano)
Elisabetta Borciani (Registro tumori Piacenza)
Lorenza Boschetti (Registro tumori Pavia)
Angelita Brustolin (Registro tumori Viterbo)
Carlotta Buzzoni (Registro tumori toscano, Istituto per lo studio, la prevenzione e la rete oncologica – ISPRO, Firenze)
Maria Caiazzo (Registro tumori Salerno)
Giuseppina Candela (Registro tumori Trapani)
Giuliano Carrozzi (Registro tumori Modena)
Luca Cavalieri D'Oro (Registro tumori Monza Brianza)
Rosaria Cesaraccio (Registro tumori Sassari)
Paolo Contiero (Istituto nazionale dei tumori, Milano)
Maria Lia Contrino (Registro tumori Siracusa)
Vincenzo Coviello (Registro tumori Barletta)
Fabio Falcini (Registro tumori Romagna)
Anna Clara Fanetti (Registro tumori Sondrio)
Stefano Ferretti (Registro tumori Ferrara)
Rosa Filiberti (Registro tumori Genova)
Rocco Galasso (Registro tumori Basilicata)
Anna Giorno (Registro tumori Cosenza-Crotone)
Iolanda Grappasonni (Registro tumori infantili Marche)
Michele Magoni (Registro tumori Brescia)
Lucia Mangone (Registro tumori Reggio Emilia)
Guido Mazzoleni (Registro tumori Alto Adige)
Anna Melcarne (Registro tumori Lecce)
Maria Michiara (Registro tumori Parma)
Aldo Minerba (Registro tumori Taranto)
Fabio Pannozzo (Registro tumori Latina)
Silvano Piffer (Registro tumori Trento)
Salvatore Pisani (Registro tumori Como)
Paolo Ricci (Registro tumori Mantova)
Massimo Rugge (Registro tumori Veneto)
Antonio Giampiero Russo (Registro tumori Milano)
Carlotta Sacerdote (Registro tumori Infantili Piemonte)
Giuseppe Sanpietro (Registro tumori Bergamo)
Salvatore Sciacca (Registro tumori integrato Catania-Messina-Siracusa-Enna)
Giorgia Stoppa (Registro tumori toscano, Istituto per lo studio, la prevenzione e la rete oncologica – ISPRO, Firenze)
Fabrizio Stracci (Registro tumori Umbria)
Antonella Sutera (Registro tumori Catanzaro)
Giovanna Tagliabue (Registro tumori Varese)
Rosario Tumino (Registro tumori Ragusa)
Mario Usala (Registro tumori Nuoro)
Francesco Vitale (Registro tumori Palermo)
Roberto Zanetti (Registro tumori del Piemonte, Province di Biella e Vercelli)

REFERENCES AND NOTES

1. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol 2017; 18(6):719-31.
2. Saletta F, Dalla Pozza L, Byrne JA. Genetic causes of cancer predisposition in children and adolescents. Transl Pediatr 2015;4(2):67-75.
3. Zhang J, Nichols KE, Downing JR. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med 2016;374(14):1391.
4. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am 2015;62(1):11-25.
5. National Cancer Institute. Childhood cancers. Available from: https://www.cancer.gov/types/childhood-cancers
6. Prüss-Ustün A, Wolf J, Corvalán C, Bos R, Neira M. Preventing disease through healthy environments: A global assessment of the environmental burden of disease from environmental risks. Geneva: World Health Organization; 2016. Available from: http://apps.who.int/iris/bitstream/handle/10665/204585/9789241565196_eng.pdf;jsessionid=B21E26E3A884FE2A69D94D2A481CEA30?sequence=1
7. World Health Organization. Effects of air pollution on children's health and development. A review of the evidence. Copenhagen (Denmark): World Health Organization, Regional Office for Europe; 2005. Available from: http://www.euro.who.int/__data/assets/pdf_file/0010/74728/E86575.pdf
8. World Health Organization. Inheriting a sustainable world? Atlas on children's health and the environment. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available from: http://www.who.int/ceh/publications/inheriting-a-sustainable-world/en/
9. Laborde A, Tomasina F, Bianchi F, et al. Children's health in Latin America: the influence of environmental exposures. Environ Health Perspect 2015;123(3):201-9.
10. World Health Organization. Don't pollute my future! The impact of the environment on children's health. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available from: http://www.who.int/ceh/publications/don-t-pollute-my-future/en/
11. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in Adolescents and Young Adults: A Narrative Review of the Current Status and a View of the Future. JAMA Pediatr 2016;170(5):495-501.
12. Bleyer A, O'Leary M, Barr R, Ries LAG (eds). Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000. Bethesda (MD): National Cancer Institute, National Institutes of Health; 2006. NIH publication 06-5767.
13. van Liedekerke M, Prokop G, Rabl-Berger S, Kibblewhite M, Louwagie G. Progress in the Management of Contaminated Sites in Europe. Report EUR 26376. Luxembourg: Joint Research Centre; 2014. Available from: https://ec.europa.eu/jrc/en/publication/reference-reports/progress-management-contaminated-sites-europe
14. European Environment Agency. Environment and human health. Joint EEA-JRC. EEA Report No 5/2013. Report EUR 25933 EN. Luxembourg: Publication Office of the European Union, 2013. Available from: https://www.eea.europa.eu/publications/environment-and-human-health/download
15. World Health Organization. Environment and health risks: a review of the influence and effects of social inequalities. Copenhagen: WHO Regional Office for Europe; 2010. Disponibile all'indirizzo: http://www.euro.who.int/__data/assets/pdf_file/0003/78069/E93670.pdf
16. Comba P. The Italian experience on contaminated sites and health: the SENTIERI Project. In: Pasetto R, Iavarone I (eds). First Plenary Conference. Industrially Contaminated Sites and Health Network (ICSHNet, COST Action IS1408). Istituto Superiore di Sanità. Rome, October 1-2, 2015. Proceedings. Rapporti ISTISAN 16/27; pp. 31-35. Available from: http://old.iss.it/binary/publ/cont/16_27_web.pdf
17. Pirastu R, Pasetto R, Zona A, et al. The health profile of populations living in contaminated sites: SENTIERI approach. J Environ Public Health 2013;2013:939267.
18. Iavarone I, Pirastu R, Minelli G, Comba P. Children's health in Italian polluted sites. Epidemiol Prev 2013;37(1) Suppl 1:255-60.
19. Santoro M, Minichilli F, Pierini A, et al. Congenital Anomalies in Contaminated Sites: A Multisite Study in Italy. Int J Environ Res Public Health 2017;14(3). pii:E292.
20. Comba P, Ricci P, Iavarone I, et al. Cancer incidence in Italian contaminated sites. Ann Ist Super Sanita 2014;50(2):186-91.
21. Iavarone I, Biggeri A, Cadum E, et al. SENTIERI KIDS: monitoring children's health in Italian polluted sites. Epidemiol Prev 2014;38(2) Suppl 1:153-57.
22. Iavarone I, Buzzoni C, Steliarova-Foucher E. Surveillance of childhood cancers in industrially contaminated sites in Europe. Abstract No. CS-28In: 39th IACR Annual Scientific Conference (IACR 2017). Utrecht (The Netherland), 17-19 October 2017. Available from: http://www.iacr2017.org/pdf/IACR_abstractboek_digitaal06oct2017_nodetailedprog.pdf
23. Italian Association of Cancer Registries (AIRTUM). Available from: www.registri-tumori.it
24. Bray F, Colombet M, Mery L et al (eds) Cancer Incidence in Five Continents, Volume XI (electronic version). Lyon: International Agency for Research on Cancer; 2017. Available from: http://ci5.iarc.fr (last accessed: April 2018).
25. Steliarova-Foucher E, Colombet M, Ries LAG, et al (eds). International Incidence of Childhood Cancer, Volume III (electronic version). Lyon: International Agency for Research on Cancer; 2017. Available from: http://iicc.iarc.fr/results/ (last accessed: April 2018).
26. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, Third Edition. Cancer 2005;103(7):1457-67.
27. AIRTUM Working Group; CCM; AIEOP Working Group. Italian cancer figures, report 2012: Cancer in children and adolescents. Epidemiol Prev 2013;37(1) Suppl 1:1-225.
28. National Cancer Institute. Surveillance, Epidemiology and End Results Program. Standard populations – 19 age groups. Available from: https://seer.cancer.gov/stdpopulations/stdpop.19ages.html
29. Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MA, Bokemeyer C. Testicular germ cell tumours. Lancet 2016;387(10029):1762-74.
30. Minichilli F, Santoro M, Bianchi F, Caranci N, De Santis M, Pasetto R. Evaluation of the use of the socioeconomic deprivation index at area level in ecological studies on environment and health. Epidemiol Prev 2017;41(3-4):187-96.
31. Pasetto R, Zengarini N, Caranci N, et al. Environmental justice in the epidemiological surveillance system of residents in Italian National Priority Contaminated Sites (SENTIERI Project). Epidemiol Prev 2017;41(2):134-39.
32. Park AS, Ritz B, Ling C, Cockburn M, Heck JE. Exposure to ambient dichloromethane in pregnancy and infancy from industrial sources and childhood cancers in California. Int J Hyg Environ Health 2017;220(7):1133-40.
33. Ortega-García JA, López-Hernández LA, Cárceles-Álvarez A, Fuster-Soler JL, Sotomayor DI, Ramis R. Childhood cancer in small geographical areas and proximity to air-polluting industries. Environmental Research 2017:156:63-73.
34. García-Pérez J, Morales-Piga A, Gómez-Barroso D, et al. Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study. Sci Total Environ 2017;579:1333-42.
35. García-Pérez J, Morales-Piga A, Gómez J, et al. Association between residential proximity to environmental pollution sources and childhood renal tumors. Environ Res 2016;147:405-14.
36. García-Pérez J, López-Abente G, Gómez-Barroso D, et al. Childhood leukemia and residential proximity to industrial and urban sites. Environ Res 2015;140:542-53.
37. García-Pérez J, Morales-Piga A, Gómez-Barroso D, et al. Residential proximity to environmental pollution sources and risk of rare tumors in children. Environ Res 2016;151:265-74.
38. Ramis R, Tamayo-Uria I, Gómez-Barroso D, et al. Risk factors for central nervous system tumors in children: New findings from a case-control study. PLoS One 2017;12(2):e0171881.
39. Llopis-Gonzalez A, Alcaide Capilla T, Chenlo Alonso U, Rubio-Lopez N, Alegre-Martinez A, Morales Suarez-Varela M. Central nervous system (CNS) cancer in children and young people in the European Union and its involvements with socio-economic and environmental factors. J Neurol Sci 2015;359(1-2):151-55.
40. COST Action on Industrially Contaminated Sited and Health Network. Avaialble from: http://www.icshnet.eu
41. International Association of Cancer Registries. Available from: http://www.iacr.com.fr
42. Steliarova-Foucher E, Stiller C, Colombet M, Kaatsch P, Zanetti R, Peris-Bonet R. Registration of childhood cancer: Moving towards pan-European coverage? Eur J Cancer 2015;51(9):1064-79.
43. International Agency for Research on Cancer. ACCIS: Automated Childhood Cancer Information System. Available from: http://accis.iarc.fr
44. Steliarova-Foucher E, Fidler MM, Colombet M, et al. Changing geographical patterns and trend in cancer incidence in children and adolescents in Europe, 1991-2010 (Automated Childhood Cancer Information System): a population-based study. Lancet Oncol 2018;19(9):1159-69.