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Cancer incidence and congenital anomalies evaluation in the contaminated sites of Sesto San Giovanni – the SENTIERI Project

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Abstract

The Italian Institute for Environmental Protection and Research defines national priority contaminated sites (NPCSs) as land where hazardous substances are likely to pose a risk to human health. SENTIERI was the first national project evaluating the health status of residents in NPCSs. We have extended, for the site of Sesto San Giovanni, the evaluation to cancer incidence and congenital anomalies (CAs). We have found an overall significant negative association between living in the NPCS and overall cancer incidence in all ages and no association in paediatric, adolescent and young adults' population. We have found an excess risk for bladder cancer, leukaemia, lymphoid leukaemia and chronic lymphocytic leukaemia in men and for lung and breast cancer in women. For the paediatric and adolescent population, we have found an excess in embryonic tumours. Total CAs were not different from expected, while we have found excesses regarding ear, face and neck, digestive system and chromosomal defects.

Key words

- national priority contaminated sites
- cancer incidence
- congenital anomalies
- epidemiological surveillance

INTRODUCTION

The health impact of contaminated sites on residents is a hot topic worldwide, especially in terms of public health decision making, as previous and existing environmental stressors can cause local and diffuse accumulation of adverse health conditions, including development of cancer and congenital malformations [1, 2]. Several countries have established projects to monitor contaminated sites [3]. In Italy, the Italian Institute for Environmental Protection and Research (ISPRA) has identified, in 2010, 57 national priority contaminated sites (NPCSs) reduced to 39 in 2013 for administrative reasons, where soil or groundwater contamination may impact on human health [4]. They are located in every Italian region and cover 1300 km^2 of aquatic environments (marine and lagoon) and 1600 km^2 of land surface. Each NPCS shows different environmental sources depending on its active or dismissed type of industrial area, landfills or incinerator.

Several approaches have been implemented for assessing the impact of NPCSs on human health [5]: defining the health profile of populations living in NPCSs [6-8] analysing the associations between environmental exposures and health outcomes [9] and surveillance of the evolving pattern of the population health profile [10]. The SENTIERI [11, 12] project (Epidemiological Study of Residents in National Priority Contaminated Sites) was the first national project studying the health profile of residents in NPCSs. For each site, overall and cause-specific mortality has been evaluated between 1995 and 2002, and excess mortality has been estimated comparing deaths among residents in a NPCS *vs* mortality experienced by the corresponding regional population. Overall, the observed mortality has exceeded the expected rate for all causes and for causes of death with a priori sufficient or limited evidence of association with the environmental exposure, especially in NPCSs located in Southern and Central Italy. In 2014, the analyses were extended to cancer incidence and hospital discharges [13] and in 2019 to congenital anomalies [14].

The NPC site of Sesto San Giovanni includes two municipalities, Sesto San Giovanni and Cologno Monzese, located in the administrative area covered by the Health Protection Agency of the Metropolitan City of Milan (ATS), the largest metropolitan population of Northen Italy. The site, which includes 122 300 inhabitants, was established by national regulations in 2000 as having two environmental sources, landfill and steel industry. The steel activity of the Falck group began in 1906 on an area previously used for agriculture

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with the production of steel and cast iron by fusion. In the years 1917-1933 the production of sheets, welded tubes and steel wire were implemented. The global crisis of steelmaking in 1971 determined the progressive decline and in 1995, the activities of the Falk steelworks closed definitively. In 1996, all the steel plants of Sesto San Giovanni were dismantled and the first processes of redevelopment of disused production areas began. The investigations carried out following the reclamation processes started in the 2000s, showed an environmental contamination of the soil and subsoil due to metal pollution and different organic compounds and the overcoming of the normative values in the aquifer for metals, hydrocarbons and organo-chlorinated compounds attributable to the site. The site has been classified by SENTIERI [12] as having a sufficient or limited level of evidence but not sufficient to establish a causal association with respiratory diseases and asthma. In the literature, a limited evidence of association has been demonstrated between hazardous waste related exposures and liver, breast, testis and bladder cancers, non-Hodgkin lymphoma, asthma and finally between landfill and congenital anomalies [8, 15, 16]. On the other hand, the relationship between landfill and malformation in the literature is widely investigated with a recurrent increased risk of congenital abnormalities, albeit not always statistically significant [17]. Breugelmans *et al*. [18] found that the SIR for lung cancer was 40% higher than average in postcode areas closer to industrial terrain of a steel plant while Bhopal [19] found no evidence to support the hypothesis that living close to these major industries led to adverse birth outcomes.

The aim of the present study is to extend, using the SENTIERI approach, the health profile of the residents in the NPCS of Sesto San Giovanni to the evaluation of cancer incidence and malformations, not present in the recently published analysis [14] due to the lack of data avaible from the two registers at the time of data collection.

MATERIALS AND METHODS

This study considers two health outcomes, cancer incidence and congenital anomalies prevalence, and compares residents in the site of Sesto San Giovanni with non-residents. Here we use routinely collected health data from the Cancer Registry of the ATS of Milan, accredited from 2016 to the International Agency for Research on Cancer (IARC), and from the Registry of Congenital anomalies (CAs) accredited from 2019 as full member to the European Association on Surveillance on Congenital Anomalies (EUROCAT) which cover the whole area of the ATS of Milan including the area of Sesto San Giovanni. The Registry of CAs includes live birth, stillbirth and Termination of Pregnancy for Anomalies (TOPFA), as required by EUROCAT. The population roster, hospital discharge records, birth certificate, death certificates and pathology reports are included in the registry's information system. The registration methods consist in a two steps process: firstly through identification of potential malformed subjects by using electronic editing, visual editing of the medico-administrative and pathology records and secondly through the consultation of medical records by registry investigators. Consultation of all medical records allows us to have as much data as possible with high quality and completeness.

Cancer incidence

The data on cancer incidence from 2007 to 2013 was selected from the Cancer Registry of the ATS of Milan, nationally accredited to the Italian Association on Cancer Registry (AIRTUM) and to the International Association of Cancer Registries (IACR). The investigated cancer sites, according to the ICD-10 classification [20], includes all cancers (excluding skin) and 35 specific sites [14]. Excess cases have been evaluated with Standardised Incidence Ratios (SIR) stratified by sex, which compares the number of observed cases with the number of expected cases if they had the same incidence rate of a standard population. For each cancer site, the expected cases have been calculated from the age and sex specific rates of the Italian North-West population between 2006 and 2010, available from the database of AIRTUM [21] between 2006 and 2010, excluding individuals resident in a municipality belonging to a NPCS.

Special attention has been given to the paediatric (0-14), adolescent (15-19) and young population (20-29 years), for which we have converted the morphology and topography ICDO-3 codes [22] in the register to the 3° International Classification of Childhood Cancer (ICCC) classification [23]. The investigated cancer sites, includes all malignant cancers and 13 specific sites [14]. Excess cases have been evaluated with SIR. Expected cases between 2006 and 2010 have been calculated from the national AIRTUM database, excluding individuals resident in a municipality belonging to a NPCS.

Each SIR was coupled with a 90% confidence interval (CI) from a Poisson regression model, if the number of cases was smaller than 100, and by Byar's approximation when greater [24].

Congenital anomalies

CAs information has been selected from the population-based registry of Milan, which includes cases with CAs among live births (up to 15 months of age), stillbirth (with gestational age ≥ 20 weeks) and TOPFA. CAs among termination of pregnancy have been collected from hospital discharge records, including admissions with codes for both termination of pregnancy and CAs. In order to identify the termination of pregnancy for foetus anomalies, for women with termination of pregnancy hospital discharge codes and genetic exams 6 months prior admission, a record linkage to the pathological anatomy has been performed. The population-based registry of the province of Milan includes cases resident in the province of Milan from 2012 to 2014. We have investigated overall CAs and 12 CAs subgroups, as defined by EUROCAT [25] and classified by ICD10-BPA codes [14, 26, 27]. Cases with multiple anomalies have been considered as a single case in the definition of total cases, while cases with only minor and unspecified anomalies [25] have been excluded. Results have been displayed as number of observed cases and prevalence

of CAs by municipality of residence of the mother. In order to compare residents with non-residents, we have calculated, for each of the CA's subgroups, the prevalence ratio (PR) between the prevalence of CAs in the site of Sesto San Giovanni and that in the overall area covered by the registry. PRs were presented with the corresponding 90% confidence interval.

In line with SENTIERI approach, we used a 90% CI in order to reduce the critical use of the CI as a surrogate of the hypothesis test [27, 28]. All analyses have been performed using SAS Software (version 9.4, SAS Institute Inc., Cary, NC, USA). For identifiability concerns, cancer and congenital anomalies' results will not be displayed for subgroups with a number of cases smaller than three.

RESULTS

In the site of Sesto San Giovanni, there have been 5565 cases of cancer between 2007 and 2013 of which 53% in men. We found an overall significant negative association with all cancers excluding skin, both for men and women with a SMR of 88 (90% CI 85-91) and 95 (90% CI 92-98), respectively *(Table 1)*. For men, we found a statistically significant increased risk in the NPCS resident for bladder's cancer (SMR 121; 90% CI 111-131), leukaemia (SMR 133; 90% CI 112-157), lymphoid leukaemia (SMR 135; 90% CI 102-175) and chronic lymphocytic leukaemia (SMR 152; 90% CI 113-201). For women, we found a statistically significant increased risk in the NPCS resident for lung (SMR 114; 90% CI 101-128) and breast cancer (SMR 112; 90% CI 106-118).

In the paediatric, adolescent and young population we observed 66 cases of cancer between 0 and 29 years of which 21 (32%) in the paediatric, 7 (11%) in the adolescent and 38 (58%) in the young adult population *(Table 2)*. We found an overall, but not statistically significant, negative association with all malignant cancers, except for the age 0-14 were resident in the NPCS were at increased risk (SMR 113; 90% CI 76-163). For the paediatric and adolescent population, there was a statistically significant increased risk only for embryonic tumours with a SIR of 262 (90% CI 114-518) and 821 (90% CI 408-1480) respectively. We did not find any increased statistically significant risk for the NPCS resident in the young-adult population. Results for lymphoid leukaemia and neuroblastoma are not displayed because the observed cases were smaller than three for all ages.

The total number of CAs between 2012 and 2014 in the NPCS was 86 out of 3529 births (according to the Italian National Institute of Statistics, ISTAT [29]) with a prevalence of 243.7 cases per 10 000 inhabitants *(Table 3)*. In the province of Milan, the total number of cases were 1485 out of 56 029 births with a prevalence of 265.0 per 10 000 inhabitants. The prevalence ratio for total CAs was thus 92 (90% CI 83-102), showing an observed number of events not different from the expected. We observed excess cases in the resident population for ear, face and neck defects (PR = 176; 90% CI 106-274), digestive system (PR = 156; 90% CI 115-203) and chromosomal defects (PR = 176; 90% CI 133-222). Results for respiratory and abdominal wall

Table 1
Number of observed cases (N), standardized incidence ratio (SIR*100), 90% confidence intervals (CI) for cancer site by gender.

	Men		Women	
Cancer sites	**N**	**SIR (90% CI)**	**N**	**SIR (90% CI)**
All cancers, excluding skin	2947	88 (85-91)	2618	95 (92-98)
Esophagus	33	99 (72-132)	5	42 (17-89)
Stomach	145	90 (78-103)	99	92 (78-109)
Colorectal	428	97 (90-105)	303	84 (76-93)
Liver	148	90 (78-104)	45	62 (48-79)
Gallbladder	36	111 (82-147)	46	109 (84-139)
Pancreas	90	92 (77-110)	115	107 (91-125)
Larynx	62	98 (78-121)	4	48 (16-109)
Lung	552	107 (99-114)	212	114 (101-128)
Bone	7	129 (60-242)	<3	
Mesothelioma	18	71 (46-106)	18	146 (95-217)
Soft tissue sarcoma	24	136 (94-191)	19	127 (83-187)
Soft tissue sarcoma*	20	129 (85-187)	16	124 (78-189)
Melanoma of skin	64	74 (59-91)	47	56 (44-72)
Breast	9	113 (59-197)	947	112 (106-118)
Uterus			159	93 (81-106)
Cervix uteri			42	97 (74-126)
Corpus uteri			113	91 (77-107)
Ovary			88	100 (83-120)
Prostate	444	65 (60-71)		
Testis	22	68 (46-97)		
Kidney and urinary tract	121	90 (77-105)	57	79 (63-99)
Bladder	398	121 (111-131)	82	102 (84-122)
Brain and other parts of the central nervous system	47	101 (78-129)	38	97 (73-127)
Thyroid	26	84 (59-117)	68	76 (62-93)
Lymphoid, hematopoietic and related tissue	281	111 (100-122)	199	92 (82-104)
Hodgkin lymphoma	20	114 (75-165)	8	52 (26-93)
Non-Hodgkin lymphoma	109	94 (80-110)	88	85 (71-102)
Myeloma	48	110 (85-140)	47	115 (89-147)
Leukaemia	102	133 (112-157)	57	101 (80-126)
Lymphoid leukaemia	41	135 (102-175)	23	107 (73-152)
Acute lymphoblastic leukaemia	5	75 (30-157)	<3	
Chronic lymphocytic leukaemia	36	152 (113-201)	21	131 (88-189)
Myeloid leukaemia	39	123 (92-160)	22	92 (62-131)
Acute Myeloid leukaemia	26	124 (87-172)	15	87 (54-134)
Chronic Myeloid leukaemia	13	121 (71-192)	7	103 (48-194)

Table 2
Number of observed paediatric, adolescent and young adults cases (N), standardized incidence ratio (SIR*100), 90% confidence intervals (CI) for cancer site

	Age classes									
	0-14 years		15-19 years		0-19 years		20-29 years		0-29 years	
Cancer sites	**N**	**SIR (90% CI)**	**N**	**SIR (90% CI)**	**N**	**SIR (90% CI)**	**N**	**SIR (90% CI)**	**N**	**SIR (90% CI)**
All malignant cancers	21	113 (76-163)	7	72 (34-136)	28	99 (71-136)	38	77 (58-101)	66	85 (69-104)
All malignant and non-malignant SNC cancers	21	103 (69-149)	7	68 (32-128)	28	92 (65-125)	38	75 (56-98)	66	81 (65-100)
All haematological tumours	9	99 (52-173)	4	92 (32-211)	13	97 (57-154)	10	81 (44-138)	23	89 (61-127)
Leukaemia	5	79 (31-166)	< 3		6	80 (35-157)	<3		7	67 (31-126)
Acute myeloid leukaemia	3	292 (80-755)	< 3		3	225 (61-581)	<3		3	140 (38-362)
Lymphomas	4	146 (50-333)	3	96 (26-247)	7	119 (56-224)	9	96 (50-168)	16	105 (66-159)
Hodgkin lymphomas	< 3		< 3		3	88 (24-228)	6	99 (43-196)	9	95 (50-166)
Non-Hodgkin lymphomas	3	223 (61-577)	< 3		4	193 (66-442)	3	103 (28-267)	7	141 (66-264)
Central nervous system tumours- malignant	< 3		< 3		< 3		<3		4	81 (28-185)
Central nervous system tumours- malignant and non-malignant	< 3		< 3		< 3		<3		4	46 (16-105)
Soft tissue and other extra osseous sarcomas	< 3		< 3		< 3		4	229 (78-525)	4	121 (41-277)
Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	< 3		< 3		3	211 (58-545)				
Thyroid carcinomas			< 3		< 3		5	59 (23-123)	5	49 (19-104)
Embryonic tumours	6	262 (114-518)	< 3		8	821 (408-1480)				

defects are not shown because the observed number of cases was smaller than three.

DISCUSSION

The evaluation of the health profile of populations living closer to industrially contaminated areas is important in the public health framework. For NPCSs characterized by single and well-defined environmental exposures, tracing an impact on health can be straightforward. This attribution is complex when the contaminated site presents multiple and heterogeneous sources of contamination. In the previous editions of SENTIERI [12,14], residents in the site of Sesto San Giovanni did not have any statistically significant risk excesses for all-cause and for principal causes of mortality for both men and women. A different pattern has been found on hospitalizations, were excess risks were found for all-cause and for respiratory diseases. Similar associations were found for the paediatric, adolescent and young adult's population.

The environmental sources characterizing the NPCS of Sesto San Giovanni, landfill and steel industry, were classified by SENTIERI as having a sufficient or limited level of evidence of association with respiratory diseases and asthma. Fazzo *et al*. [15] from a literature review, evaluated as limited the evidence of a causal association between hazardous waste related exposures and liver, breast, testis and bladder cancers, non-Hodgkin lymphoma and asthma and finally overall and specific congenital anomalies. Here we found an overall negative association between living in the NPCS and overall cancer incidence for all ages, and a number of observed cases not different from the expected for the paediatric, adolescent and young adults' population. On the other hand, we found an excess risk for bladder cancer in men and for breast cancer in women, cancers consistent with the environmental characteristic of the site.

Table 3
Number of observed cases (N), prevalence ratio (PR*100), 90% confidence intervals (CI) for Congenital Anomalies, total and cause specific

Type of anomalies	**N**	**PR (90% CI)**
Nervous system	10	136 (95-183)
Eye	4	151 (88-260)
Ear, face and neck	5	176 (106-274)
Congenital heart defects	39	84 (71-98)
Oro-facial clefts	4	84 (44-130)
Digestive system	13	156 (115-203)
Urinary system	5	51 (30-78)
Genital	11	116 (83-155)
Limb	12	102 (76-137)
Chromosomal	16	176 (133-222)
Total	86	92 (83-102)

In order to define the overall health profile of the population living in the site of Sesto San Giovanni, we presented SIRs for all the causes investigated. We found risk excess for Leukaemia, Lymphoid leukaemia and chronic lymphocytic leukaemia in the adult's population. Even if they are not directly referable to the environmental characteristic of the site, these causes are defined by SENTIERI as inadequate to infer the presence but also the absence of a causal association. Furthermore, we found a significant association between living in the NPCS and lung cancer in women. Nevertheless, lung cancer incidence has a significant increasing trend in women since early two thousands at national and international level, more consistent in urban areas and due to the increase in smoking habits in women. Not having found an association in the male gender further supports this consideration. Negative associations in adults were found for melanoma of skin for both genders, prostate and testis for men and kidney and urinary tract, thyroid and Hodgkin lymphoma for women. For the young adults' population, negative associations were found for all malignant and non-malignant CNS cancers. Total CAs were not different from expected in Sesto San Giovanni's residents, while we found excesses for ear, face and neck defects, digestive system and chromosomal defects.

Negative associations were found for congenital heart defects and urinary system. It is important to remember that the identification of Sesto San Giovanni as a National contaminated site goes back to 2010 and it referred to a steel industry that closed in 1996. Furthermore, these results showed a plausible effect of air pollution, which is a well-known problem of the municipalities, such as Sesto San Giovanni, localized in the north of the Milan province. In particular, the possible correlation between ambient air pollution and orofacial cleft anomalies in new-borns was recently reported in a systematic review and meta-analysis but only ozone showed the strongest correlation with cleft lip and cleft palate anomalies [30].

Comparing NPCSs is difficult given the different sources that characterized each site. In the NPCS of Terni-Papigno, which share the same sources of exposure with Sesto San Giovanni, the SENTIERI project found an association with lung cancer in both men and women, with breast cancer in women and with non-Hodgkin lymphoma in men. Breugelmans *et al*. [18] found that the SIR for lung cancer was 40% higher than average in postcode areas closer to industrial terrain of a steel plant.

As all ecological studies based on routinely collected data, this procedure presents some biases. First, data quality is taken for granted. Here, we used data from the Cancer Registry of the ATS of Milan and from the CAs Registry accredited and validated from IARC and EUROCAT respectively. Furthermore, when reading these results, we have to be aware that exposure is defined from municipality where aggregated data can suffer from the ecological fallacy, especially in relatively small populations where limited number of cases per cancer sites may affect statistical power. However, the selection of diseases on the basis of a priori evidence should limit the typical biases of descriptive studies involving data dredging and multiple testing [5].

CONCLUSIONS

Assessing the health impact of NPCSs on residents is a fundamental priority of public health organizations, as previous and existing environmental stressors can cause local and diffuse accumulation of adverse health conditions. Once the risk has been assessed, the next challenge is to implement policies capable to respond to this need, especially analysing the associations between specific environmental exposures and the health outcomes detected. Public health organizations are even more challenged on environmental issues as the demand for participation has increased, transforming ordinary concerns in public requests where citizen play the role of principal actors.

This work adds necessary information on the health profile of a population defined as susceptible by national regulations. When new information are available for Public health organizations, at delayed times in respect to the release of scientific evidence, it is necessary to communicate them in order to complete and integrate the knowledge, especially when it comes from environmental issues.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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