Cancer incidence in Priolo, Sicily: a spatial approach for estimation of industrial air pollution impact

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Abstract

The territory around the industrial Sicilian area of Priolo, Italy, has been defined as a contaminated site (CS) of national priority for remediation because of diffuse environmental contamination caused by large industrial settlements. The present study investigates the spatial distribution of cancer into the CS territory (period 1999-2006). Different geographical methods used for the evaluation of the impact of industrial air pollutants were adopted. Using the database of Syracuse Province Cancer Registry, gender-specific standardised incidence ratios were calculated for 35 tumour sites for the CS overall and for each municipality included in the CS. A cluster analysis for 17 selected neoplasms was performed at micro-geographical level. The identification of the priority index contaminants (PICs) present in environmental matrices and a review of their carcinogenicity have been performed and applied in the interpretation of the findings. The area has a higher cancer incidence with respect to the provincial population, in particular excess is registered among both genders of lung, bladder and breast cancers as well as skin melanoma and pleural mesothelioma and there is an *a priori* evidence of association with the exposure to PICs. The study highlights the need to provide different approaches in CSs where several exposure pathways might be relevant for the population. The presence of potential sources of asbestos exposure deserves specific concern.

Introduction

The European Environmental Agency (EEA) estimates 342,000 contaminated sites (CSs) in the 33 members and six cooperating countries, on the basis of the soil contamination regulation; one third of them has already been identified and about 15% have been remediated (van Liedekerke *et al.*, 2014). In Europe, the World Health Organization (WHO) has recently developed a comprehensive approach aimed at assessing the health status of populations resident in contaminated sites (WHO, 2013), including recommendations for epidemiological surveillance programmes.

In Italy, the criteria for definition of CSs of national concern for remediation to be included in the National Priority List, were firstly defined in 1998 and subsequently updated in 2006. Currently, 39 Italian national priority list CSs (NPCSs) have been defined and included in the national remediation programme. Among them, the CS of Priolo in Sicily was already identified in 1998 and confirmed in the most recent national framework decree (152/2006). The site of Priolo is characterised by a diffuse environmental contamination due to the presence of large industrial settlements that in the last decades has caused a progressive contamination of the different environmental compartments. Toxic, persistent and bio-accumulable compounds, such as heavy metals, polychlorinated biphenyls (PCBs), dioxins and polycyclic aromatic hydrocarbons (PAHs) were detected and the past and present exposure to Volatile organic compounds (VOCs) was ascertained (Beccaloni *et al.*, 2014).

The overall area included in the Priolo CS was considered in the national programme of epidemiological surveillance in contaminated sites, the *SENTIERI* Project (Pirastu *et al.*, 2013, 2014). The incidence of all cancers in the population living in the Priolo CS showed an excess in both genders with respect to the pool of cancer registries of

central and southern Italy; specific neoplasms in excess included tumours of the liver and pancreas and mesothelioma. In the analysis by gender, an excess of tumours of the lung, bladder and central nervous system were detected in men and so was the case for colon-rectum, breast and uterus in women (Pirastu *et al.*, 2014). Increases of mortality and hospitalisation for specific neoplasms were found in the population living in the Priolo CS also with respect to the neighbouring municipalities and the Sicilian regional rates (Dipartimento Attività Sanitarie ed Osservatorio Epidemiologico. Assessorato Regionale della Salute, 2012). The present study investigates the incidence of tumours with respect to the Province of Syracuse, Sicily. These populations are more similar, in terms of access to healthcare, quality of diagnosis, lifestyle, *etc.*, than that used in previous studies. We emphasise the types of cancer with a possible positive association with the contaminants, defined as priority index contaminants (PICs), detected in the area considering the following criteria: quality of information, presence in different environmental matrices, levels of detected concentrations, diffusion of the contamination(s) in the areas with risk for population exposure. Furthermore, the distribution of cancer cases in the CS territory under study was examined taking into account the impact area of atmospheric pollutants emitted by the plants and taking into account that environmental pressure due to the concurrent presence of multiple carcinogenic agents may affect the resident population through different routes of exposure and pathogenic mechanisms. The present study is mainly focused on inhalation exposure to carcinogenic pollutants emitted by industrial sources that can be the object of a spatial analysis as well as testing the hypothesis of clustering.

Materials and Methods

The study area extends for about 14 km along the Sicilian southeastern coast including two refineries, three petrochemical plants, a liquid gas production plant, an incinerator of harbour waste, a cement plant, a former asbestos-cement plant (Eternit) and several landfills comprising hazardous waste. Priolo CS, including the municipalities of Augusta, Priolo, Melilli and Syracuse, covers a total area of 159 km^2 (about 58 of land and 100 of sea) and comprises the harbour areas of Syracuse and Augusta Bay (Figure 1).

Environmental contamination

In order to identify the main contaminants present in the area, environmental data made available by the Sicilian Region Environmental Protection Agency (ARPA) were considered. Since the present study is based on the residence of cancer patients, special attention was given to the spatial patterns of air pollution for which several data sources were considered: air quality monitoring network, atmospheric emissions from the industries and bio-monitoring of lichens for metal inclusions. An atmospheric dispersion model (ISCST3) (Lakes Environmental, 2013) was applied to industrial emissions, taking into account the meteorological data and terrain heights of the area, in order to obtain concentration maps of sulfur dioxide (SO$_2$), nitrogen oxides (NOx) and particulate matter (PM) emitted by industrial point sources, and to investigate their impact on air quality. About 100 point sources were identified and emission data of specific contaminants were acquired. The atmospheric dispersion was simulated on a grid of 111x150 regular receptors, over an area of 22 km x 39 km, and on seven discrete receptors corresponding to the position of the monitoring stations. The simulated concentrations of SO$_2$ were compared with the SO$_2$ concentrations measured by the air quality-monitoring network

(period 2008-2012), with the aim of verifying the reliability of the dispersion model. The annual investigations (2006 and 2007) of the lichen bio-monitoring analysed the following heavy metals in samples from 36 stations: arsenic, cadmium, chromium, mercury, nickel, vanadium and lead (ARPA Sicilia, 2008). The annual averages of the contaminants were subject of a statistical analysis and an ordinary Kriging method. The latter is a geostatistical estimator that infers the value of a random field at an unobserved location from samples producing a prediction surface that provides measures of the certainty or accuracy of the predictions (Johnston *et al.*, 2001; Cressie, 2002). The model involved data pre-processing to remove spatial trends and data transforming in a Gaussian distribution, whose application was feasible only for vanadium and nickel.

Evaluation of priority index contaminants carcinogenicity

Based on a review of the environmental contamination data made available by the ARPA, a list of PICs was identified, on the basis of the criteria described above. The epidemiological evidence of the carcinogenicity of identified PICs was evaluated following the procedure described by Zona *et al.* (2014), which considers information about the carcinogenicity of pollutants elaborated by several scientific institutions (such as the International Agency for Research on Cancer, the Agency for Toxic Substances and Disease Registry, the US Environmental Protection Agency, the European Food Safety Authority). The tumour sites were grouped on the basis of the strength of the association with exposure to the PICs investigated: group a) - sufficient evidence; group b) - limited evidence; group c) - positive
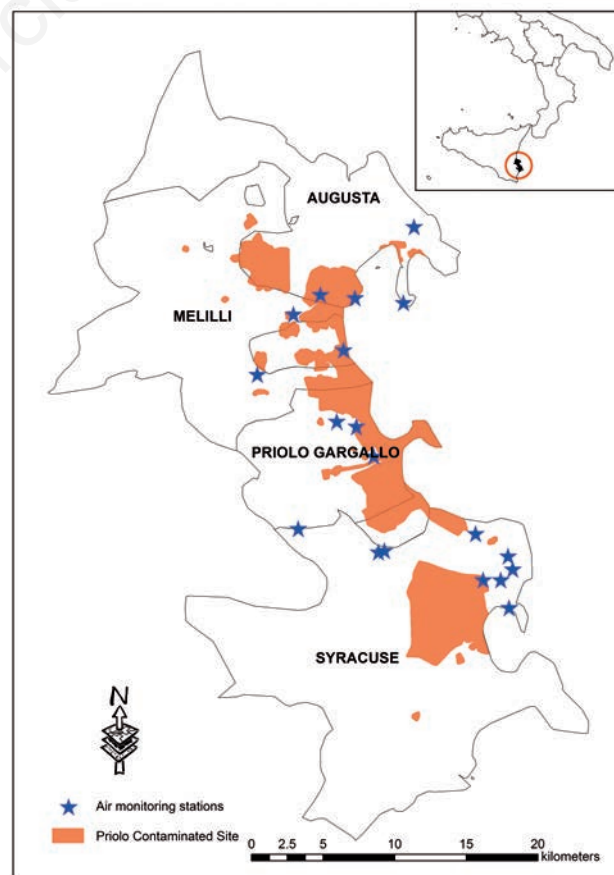

Figure 1. National priority contaminated site of Priolo, Sicily.

association (*i.e.*, the neoplasms for which the strength of evidence was not available but where a positive association was reported).

Cancer incidence data and epidemiological analysis

The present study was based on data of the Cancer Registry of Syracuse Province that includes the four municipalities constituting Priolo CS. The Registry is part of the Italian Network of Cancer Registries (AIRTum) and is certified by the International Agency for Research on Cancer (IARC) (Curado *et al.*, 2007; Madeddu *et al.*, 2009). The Registry certifies all cases living in Syracuse Province at the time of diagnosis (period 1999-2006 - at the start of the present investigation). To obtain information on the burden of cancer diseases in the population, 35 neoplasms (or groups of neoplasms) classified on the basis of topographic criteria [International Classification Diseases for Oncology 3rd edition (ICD-O-3) codes], were considered. Subjects resident in the investigated municipalities and diagnosed with one of the selected neoplasms in the time-window of the study identified in Cancer Registry database and their addresses at the time of diagnosis were obtained from Municipal Registrar Offices.

Standardised incidence ratios (SIRs), and their corresponding 95% Confidence Intervals for each selected cancer site, were computed for the Priolo CS overall area and for each municipality included in the CS with respect to Syracuse Province. The provincial reference rates were calculated on the basis of the cancer cases diagnosed in the period 1999-2006 and the population living at 1/1/2003 multiplied by the eight-year period of observation; the residents in the study area were excluded. The analyses, standardised by age-classes, were performed separately by gender, using the STATA statistical software (StataCorp, 2010). Subsequently, cluster analysis was performed to investigate the spatial aggregation of the cases into the study area aiming at the census-tracts, the smallest administrative units for which resident population data are available. The analysis was carried out for those neoplasms, for which an etiological role of environmental exposures was hypothesised on the basis of scientific evidence available at the time of study design: cancer of the liver, pancreas, larynx, lung, testis, bladder, thyroid, pleural mesothelioma, melanoma of skin and lymphoematopoietic system neoplasms, non-Hodgkin lymphomas, Hodgkin's disease, leukaemias (lymphoid leukaemias, acute and chronic; myeloid leukaemias, acute and chronic). Clustering was tested both including and excluding Syracuse Municipality, the most populated town in the study area; the analysis of liver cancer was, however, carried out excluding Syracuse because of the unavailability of residence information for the cases living in this municipality. The address of each case at time of diagnosis was mapped in a geographical information systems (GIS) software including the geographic boundaries of census-tracts and each case was attributed to the corresponding census-tract. The population residing in each census-tract was computed on the basis of 2001 Census population data, multiplied by eight, the years of the observation period. Spatial clusters of cases were identified by using SatScan software, version 6 (Kuldorff, 1997) assuming a Poisson model for the distribution of cases in each census-tract. The adopted spatial scan statistics procedure employs a circular window whose radius was fixed with a maximum of 3 km centred at each step on one census-tract, identified by the x, y coordinates of its geographic centroid. Significant levels were fixed at P<0.1.

Results

The review of the environmental data showed a diffuse, widespread chemical contamination in all environmental compartments with high concentrations of hazardous substances in soil, groundwater and fisheries in the whole Priolo CS area. However, there was no available information on some highly toxic micropollutants (*i.e.* polycyclic aromatic hydrocarbons, dioxin, metals) in the atmospheric particulate matter.

Environmental contamination

The analysis of air quality monitoring data shows that hourly SO_2 concentrations are well associated with industrial emissions detecting higher concentrations in concordance with the wind directions blowing from industrial sources. For NOx and PM_{10} (particulates matter with aerodynamic diameter ≤10 micrometers) the contribution from other sources (typically traffic emissions) produces a background value, which does not allow to point out correlations with industrial emissions; only in two monitoring stations higher concentrations of NO_2, NOx and benzene suggest an association with the wind blowing from plants. The comparison of the simulated and observed SO_2 concentrations showed a good agreement. Figure 2 shows the impact area of air dispersion model of SO_2 industrial emissions.
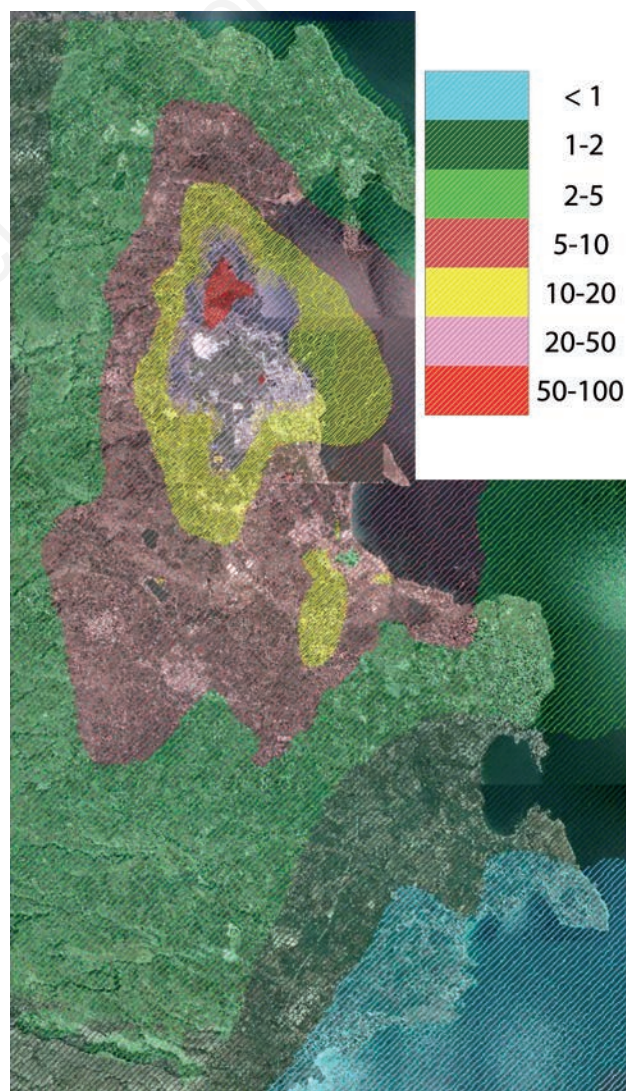
Figure 2. Air dispersion model of SO_2 industrial emissions ($\mu g/m^3$).

The study on metal inclusion in lichens highlighted a contamination of industrial origin for zinc, copper, mercury, cadmium and chromium. The statistical analysis showed a specificity of metal accumulation in different stations, generating the hypothesis of different sources of pollution. The stations, which presented the highest values for several of these contaminants, are located in the southern area of Augusta and the western area of Melilli. Figure 3 shows the results of the Kriging model for vanadium and nickel lichen bio-monitoring, the agents for which the model was fitted. The distribution of the two contaminants is similar, with the highest values concentrated in the industrial area [maximum: 7.9 mg/kg dry weight (dw), vanadium; 9 mg/kg dw, nickel] and a distribution in accordance with the prevailing wind directions. In summary, the southern area of Augusta municipality, downwind of industrial emissions, and the part of Priolo municipality nearest to the industrial area, appear to be mainly affected by atmospheric dispersion of the industrial emissions.

Contamination of soil, groundwater and sediments was also considered in order to estimate the whole environmental burden present in the area. Indeed, chemical contamination of all environmental compartments was evident with concentrations of various hazardous substances present at several orders of magnitude above the threshold values allowed by environmental and health regulations. Because of the massive contamination of soil, groundwater and sediments, the risk of exposure to hazardous substances through different pathways, other than inhalation, such as drinking water, ingestion of local agricultural products including fisheries, was also hypothesised. On this ground, a number of PICs, as defined in the methodology section, were evaluated (Table 1).

Evaluation of contaminant carcinogenicity

Table 2 shows the cancer sites or tissues with a positive association with one, or more PIC(s) on the basis of the evaluation of international scientific institutions documents (ECHA, 2013; IARC, 1993, 1997, 1999, 2001, 2006a, 2006b, 2012a, 2012b, 2014b; NTP 2014; USEPA, 1991, 1998, 2010, 2011, 2013); as previously stated, neoplasms or tumour sites were grouped on the basis of strength of association.

Group a) (sufficient evidence): all malignant neoplasms, stomach, liver, lung, cutaneous melanoma, kidney, urinary bladder and acute myeloid leukaemia/acute non-lymphocytic leukaemia.

Group b) (limited evidence): malignant neoplasms of biliary tract, breast, prostate, soft tissue sarcomas and non-Hodgkin lymphomas.

Group c) (positive association): multiple myeloma, acute and chronic lymphocytic leukaemias.

Cancer incidence data and epidemiological analyses

The epidemiological investigation considered 2552 cases (1808 men and 744 women) living in the Priolo CS area at the time of diagnosis, which had a diagnosis of neoplasm in one of the 34 selected cancer sites in the 1999-2006 period. In the same period, 15,789 total cancer cases (9097 males and 6692 females) were diagnosed in the province of Syracuse. The population served by the Cancer Registry of Syracuse Province constituted 396,517 inhabitants (194,104 men and 202,413 women) at 1/1/2003. The cases under study are distributed in the four municipalities as follows: 549 in Augusta (376 men and 173 women), 131 in Melilli (95 men and 36 women), 138 in Priolo (101 men and 37 women) and 1734 in Syracuse (1236 men and 498 women). Tables 3 and 4 show the SIRs in the overall CS area and in each municipality, respectively. Among malignancies with a sufficient *a priori* evidence of association with contaminants (group a), all malignant neoplasms, lung and urinary bladder cancers and cutaneous melanoma were in excess of expected numbers in both genders in the CS overall area. At the municipal level, an increased incidence of all malignant neoplasms in both genders was observed in Syracuse and in Augusta, whereas this finding was only found to be present in the male population in Priolo. The increase of lung cancer was also evident in both genders in Syracuse municipality and in the male population of Augusta.

Table 1. Priority index contaminants in the area of the Priolo contaminated site.

	Industrial soil	Groundwater	Pine trees needles°	Lichens°	Sediment#	Fish products
Arsenic	x	x	x	x	x	
Cadmium	x			x		x
Chromium total	x	x	x	x	x	
Chromium VI	x	x				
Mercury	x	x		x	x	x
Lead	x	x	x	x	x	x
Nickel		x	x	x		
Vanadium	x	x	x	x	x	
1,2Dichloroethane	x	x				
Benzene	x	x				
Vinyl Chloride	x	x				
Hexachlorobenzene	x	x			x	x
Tetrachloroethylene	x	x				
Xylene	x	x				
Trichloroethylene		x				
Hydrocarbons C<12	x					
Hydrocarbons C>12	x					
Hydrocarbons total		x				

°No regulatory values are available for pine tree needles and lichens; #marine coastal area.

Cutaneous melanoma incidence was in excess in both genders in Syracuse and among women in Augusta. Urinary bladder tumours were found in excess in Syracuse in both genders. Malignant liver neoplasms were in excess among females in the CS overall area and in Augusta, kidney tumours in males (CS overall area) and females (Syracuse). Stomach cancer showed a decrease with respect to the reference population among men in Syracuse. However, the incidence of acute myeloid leukaemia/acute non-lymphocytic leukaemia did not depart from the expected, neither in the whole CS nor in each municipality. Regarding incidence of malignant tumours with a limited *a priori* evidence of association with contaminants (group b), increased numbers were observed for breast cancer in both genders in the CS overall area, in Syracuse and in females in Augusta. Prostatic cancer was in excess in CS overall area and in Syracuse and Priolo municipalities. Increases in Syracuse male population were found for non-Hodgkin lymphomas and chronic lymphocytic leukaemia; the latter increased also among men in the CS overall area.

The increases of pleural mesothelioma observed in both genders in the CS overall area as well as all municipalities, except Melilli, deserve particular mention due to the occupational exposure to asbestos, which was documented both in Syracuse (former asbestos-cement plant) and in Augusta (refineries, chemical industries, shipbuilding and repair industries).

The cluster analysis showed significant results mainly in Syracuse, the most populated town of the study area, except a cluster of pancreas tumour found among women in Augusta municipality. In the analysis without Syracuse, significant clusters were located in one sub-area of Augusta, which is affected by atmospheric industrial emissions. Out of the cancer types of group a) (with a sufficient *a priori* evidence of association with PICs present in the CS), lung cancer [neoplasm also in group c), because of the association with benzo(a)pyrene] constituted significant clusters in both genders in Syracuse and among women in Augusta (the latter in the analysis without Syracuse municipality) (Figure 4). Non-Hodgkin lymphomas, with a limited *a priori* evidence of association with dioxins, PCBs and trichloro-ethylene (group b) and a positive association with benzene and tetrachloroethylene (group c), appeared as a significant cluster among men in Syracuse; only one cluster was found in Priolo census-tracts that consisted of lymphocytic chronic leukaemia (diseases for which an association with present contaminants was reported, group c) among men (Figure 5). Pancreatic and thyroid cancers presented significant clusters (Figure 6), but the *a priori* evaluation did not offer clues for an association with PICs detected in study area. In summary, most examples of increased cancer incidence were found to be located in the municipalities of Syracuse and Augusta with only specific neoplasms (lung in both genders, Hodgkin and non-Hodgkin lymphomas in only men, and myeloblastic, chronic leukaemias in only women) grouped in specific subareas of Syracuse municipality.
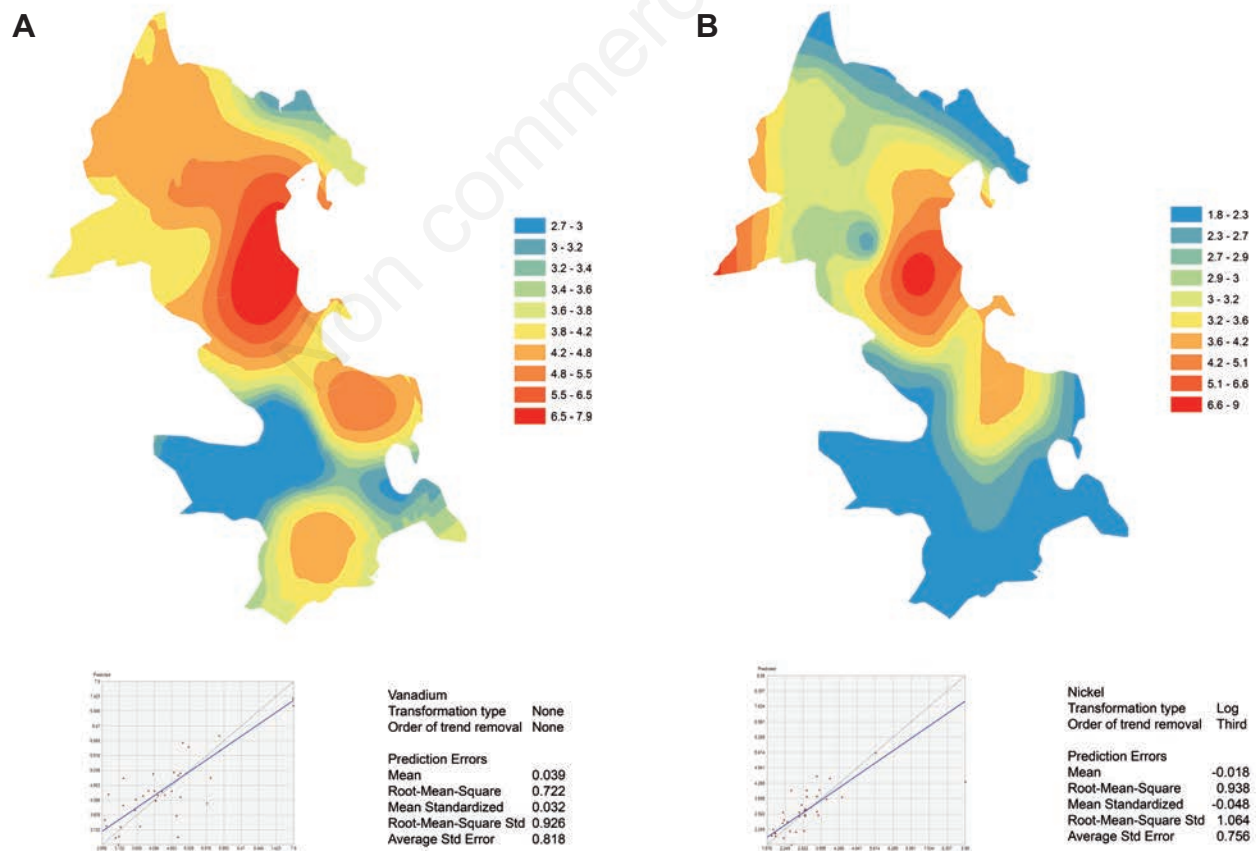
Figure 3. Kriging model maps of vanadium (A) and nickel (B).

Table 2. Evaluation of carcinogenicity of priority index contaminants with an *a priori* evidence of positive association with investigated neoplasms.

Type of malignant neoplasm	Arsenic	Benzene	Benzo[a]-pyrene	Cadmium	Chromium VI	Dioxins°	Nickel compounds	Lead and inorganic compounds	PCB	Tetrachloro-ethylene	Trichloro-ethylene	Vinyl chloride
All cancer sites						Sufficient evidence						
Stomach								Sufficient evidence				
Liver	Limited evidence										Limited evidence	Sufficient evidence
Trachea, lung bronchia	Sufficient evidence		Association	Sufficient evidence	Sufficient evidence	Limited evidence	Sufficient evidence					
Melanoma of the skin									Sufficient evidence			
Breast									Limited evidence			
Prostate	Limited evidence			Limited evidence								
Bladder	Sufficient evidence		Association									
Kidney, other urinary organs	Limited evidence			Limited evidence							Sufficient evidence	
Soft tissue sarcoma						Limited evidence						
Non-Hodgkin lymphomas		Association				Limited evidence			Limited evidence	Association	Limited evidence	
Multiple myeloma		Association								Association		
Lymphoid leukaemias Acute lymphocitic leukaemias		Association										
Chronic lymphocytic leukaemias		Association										
Acute myeloblastic leukaemias		Sufficient evidence										

PCB, polychlorinated biphenyl. °2,3,7,8-TCDD.

Discussion

In light of the characteristics of the present investigation being based on a geographical study design, the air contamination was primarily taken into account to evaluate the impact of sub-areas as the study of wind directions and pollution is straightforward. However, there are reasons to believe that other routes of exposure, such as drinking water and ingestion of fish and food, might be just as relevant. The population has probably been exposed to a mixture of pollutants by different routes and appropriate exposure modelling and risk-assessment procedures should be implemented in order to assess their relative contribution.

A limitation of the present study is that it mainly focused on inhalation exposure to carcinogenic pollutants emitted by industrial sources that can be the object of a spatial analysis as well as testing the hypothesis of clustering. Other exposure pathways (*e.g.* diet, occupation) could not be appropriately dealt with by the spatial approaches adopted in the present investigation, but may nevertheless have significantly contributed to the overall burden of cancer. With regard to the epidemi-

ological results, it should be considered that all the selected neoplasms have a multifactorial etiology, which is not always completely known. The study design did not permit to have information about individual occupational and environmental exposures patterns, lifestyle and socioeconomic conditions. For these main reasons, the role of factors other than environmental chemical exposure cannot be ruled out.

The different approaches used for investigate the spatial variability of concentrations of atmospheric industrial pollutants are mutually consistent. The value of Kriging in supporting the inhalation exposure assessment in industrial areas has recently been discussed (Vicedo-Cabrera *et al.*, 2013). The results, showing the highest values around polluting industries are in agreement with prevailing wind directions and confirm that the air quality of the CS areas is affected by industrial atmospheric emissions. In particular, specific sub-areas, in south-western part of Augusta and in part of Priolo municipality seem to be particularly affected by the impact of air pollutants emitted by industries.

The reported increased cancer numbers require a preliminary consideration. The process of environmental characterisation of this area has generated a set of cancer sites, for which *a priori* hypotheses of etiological interest based on sufficient or limited evidence of association

Gender	Radius (km)	census-tracts number	Obs	Exp	RR	p-value
Women	1.3	142	52	31.19	2.347	0.0283
Men	0.35	15	27	6.88	4.068	0.0003

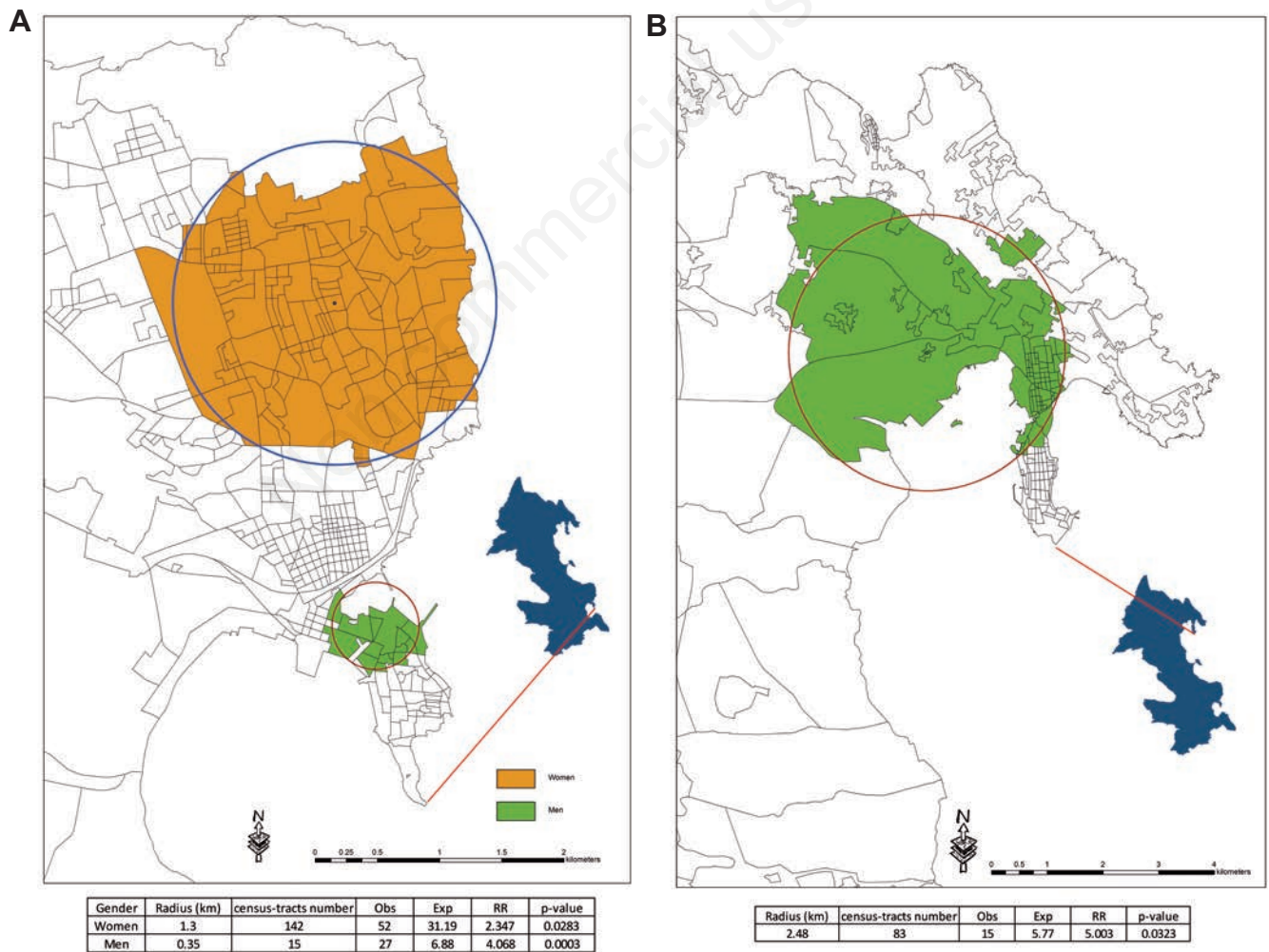| Radius (km)	census-tracts number	Obs	Exp	RR	p-value
2.48	83	15	5.77	5.003	0.0323

Figure 4. Significant clusters of lung cancer in women and men including Syracuse (A), and in women excluding Syracuse (B).

with specific contaminants (PICs) detected in the area are available. The observation of excess incidence in these cancer sites must be regarded as being most informative in terms of causal reasoning. The observed increases in the number of cancer are consistent with previous epidemiological studies on the population living in the Priolo CS. In the present study the increased cancer occurrences were detected in relation to the provincial population, and that is more similar to the population at study than the reference used in previous studies, such as those of the pool of Cancer Registries of Central and Southern Italy (Pirastu *et al.,* 2014). In particular, lung cancer is associated with sufficient evidence to exposure to specific metals (arsenic, cadmium, hexavalent chromium and nickel compounds) (IARC, 2014a), with limited evidence to 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD)

(IARC, 2014b) and an association with benzo(a)pyrene has been reported (USEPA, 2013). Cutaneous melanoma is associated with sufficient evidence to PCBs exposure (IARC, 2014c). Urinary bladder cancer is associated with sufficient evidence arsenic exposure and with limited evidence to tetrachloroethylene and an association has been reported with benzo(a)pyrene (IARC, 2014a, 2014b; USEPA, 2013). Limited evidence has been reported for the association between prostatic cancer and exposure to arsenic and cadmium (IARC, 2014a); for chronic lymphocytic leukaemia an association has been reported with exposure to benzene (IARC, 2012b). The increased occurrence of breast cancer found in both genders have to be highlighted. Male breast cancer is a rare disease and the increase found in the present investigation, based on 13 cases, deserves particular attention: in fact,

Table 3. Standardised incidence ratios in Priolo contaminated site, overall area (1999-2006).

Type of malignant neoplasm	ICD-O-3 code	Men Obs	SIR	95%CI	Women Obs*	SIR	95%CI
All malignant neoplasms	C00-C043, C45-C96, D090	3426	1.20	1.16-1.24	2732	1.14	1.10-1.18
Oesophagus	C15	16	0.85	0.48-1.37	5	0.68	0.22-1.58
Stomach	C16	108	0.83	0.68-1.00	59	0.89	0.67-1.14
Colon-rectum	C18-21	422	1.18	1.07-1.30	360	1.05	0.94-1.16
Liver	C22	167	1.10	0.94-1.28	95	1.35	1.10-1.65
Gallbladder and biliary tract	C23-24	46	1.18	0.86-1.57	69	1.20	0.93-1.52
Pancreas	C25	108	1.35	1.10-1.62	107	1.46	1.19-1.76
Larynx	C32	91	1.48	1.19-1.82	1	0.14	0.00-0.76
Trachea, bronchus and lung	C33-34	609	1.23	1.13-1.33	109	1.23	1.01-1.48
Mesothelioma of pleura	C45	38	2.23	1.58-3.06	9	2.21	1.01-4.19
Connective and soft tissue	C49	18	0.77	0.46-1.21	13	0.72	0.38-1.22
Melanoma of skin	C43	64	1.39	1.07-1.78	66	1.96	1.51-2.49
Bone	C40-C41	9	0.91	0.42-1.73	6	1.40	0.51-3.05
Breast	C50	13	2.00	1.06-3.42	814	1.15	1.07-1.23
Uterus	C53-C54				216	0.89	0.78-1.02
Cervix of uterus	C53				51	0.77	0.58-1.02
Corpus of uterus	C54				165	0.94	0.80-1.09
Ovary	C56				97	1.05	0.85-1.28
Prostate	C61	494	1.22	1.12-1.34			
Testis	C62	44	1.40	1.02-1.89			
Bladder	C67, D090	490	1.19	1.08-1.30	84	1.57	1.25-1.94
Kidney and other urinary organs	C64-C66, C68	87	1.30	1.04-1.60	39	1.31	0.93-1.79
Central nervous system	C70-C72	79	1.52	1.20-1.89	47	1.02	0.75-1.36
Thyroid gland	C73	39	1.28	0.91-1.75	151	1.17	0.99-1.37
Lymphohemopoietic system	C81-C96	301	1.15	1.02-1.28	213	1.08	0.94-1.24
Non-Hodgkin lymphomas	C82-85, C96	114	1.10	0.90-1.32	87	1.04	0.83-1.28
Hodgkin lymphoma	C81	26	1.36	0.89-1.99	23	1.37	0.87-2.05
Myeloma	C88, C90	55	1.12	0.84-1.45	44	1.24	0.90-1.66
Leukaemias	C91-C95	106	1.17	0.96-1.42	59	0.98	0.74-1.26
Lymphoid leukaemias	C910-C911	48	1.50	1.10-1.98	24	0.95	0.61-1.42
Acute lymphoblastic leukaemia	C910	13	0.93	0.49-1.58	10	1.17	0.56-2.16
Chronic lymphocitic leukaemia	C911	35	1.94	1.35-2.70	14	0.84	0.46-1.41
Myeloid leukaemias	C920-C921	43	1.12	0.81-1.51	24	1.15	0.74-1.71
Acute myeloblastic leukaemia	C920	24	1.02	0.65-1.51	14	1.03	0.56-1.72
Chronic myeloid leukaemia	C921	19	1.30	0.78-2.02	10	1.40	0.67-2.57

ICD-O-3, International Classification Diseases for Oncology, 3rd edition; Obs, observed cases; SIR, standardised incidence ratio; 95%CI, 95% confidence interval.

Radius (km)	census-tracts number	Obs	Exp	RR	p-value
1.7	198	46	26.44	2.272	0.0627

Radius (km)	census-tracts number	Obs	Exp	RR	p-value
2.16	4	3	0.13	45.782	0.0393
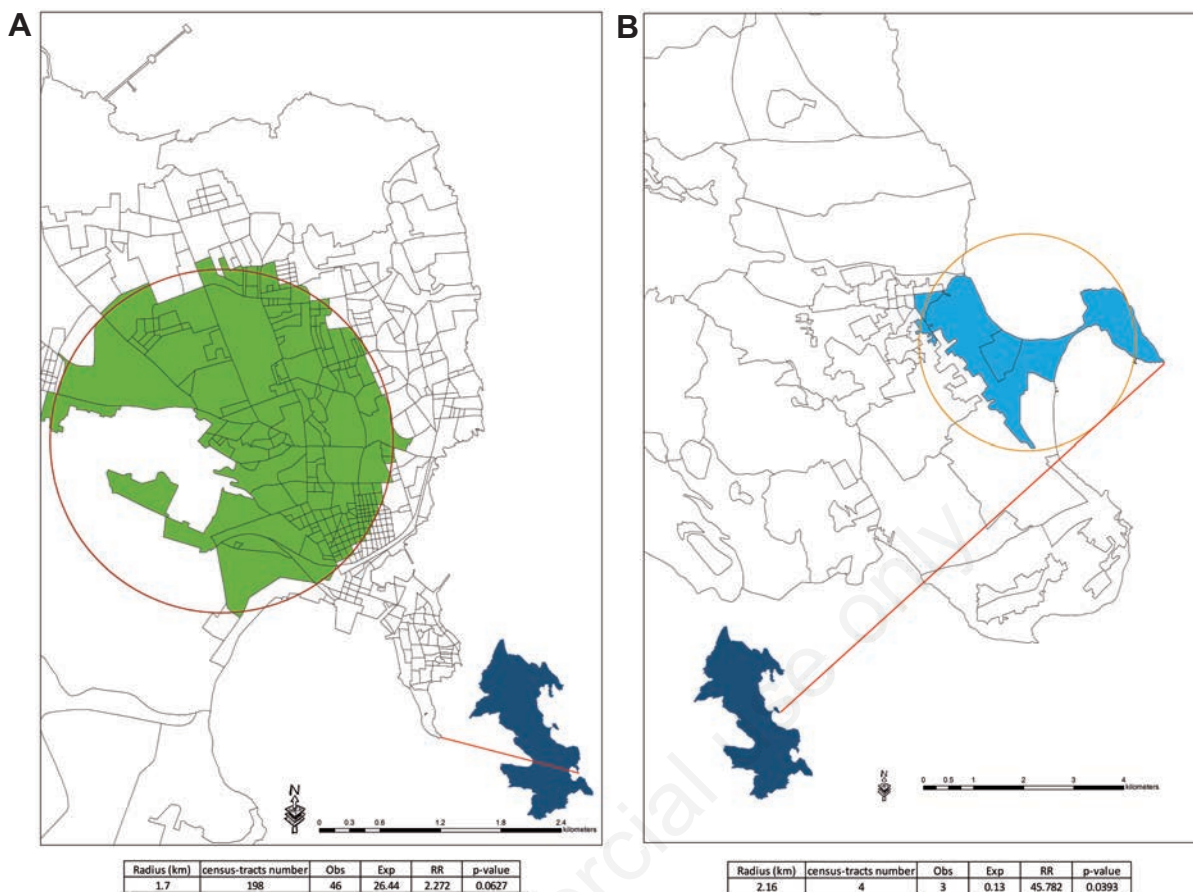
Figure 5. Significant clusters of non-Hodgkin lymphoma in men including Syracuse (A) and of lymphocytic chronic leukaemia excluding Syracuse (B).

Cluster	Radius (km)	census-tracts number	Obs	Exp	RR	p-value
1	0.07	2	4	0.17	24.006	0.037
2	0	1	2	0.01	145.029	0.0847

Radius (km)	census-tracts number	Obs	Exp	RR	p-value
0.14	7	8	1.26	7.62	0.0137

Figure 6. Significant clusters among women of pancreas cancer excluding Syracuse (A and B) and of thyroid cancer including Syracuse (C).

Table 4. Standardised incidence ratios in Priolo contaminated site, by municipality (1999-2006).

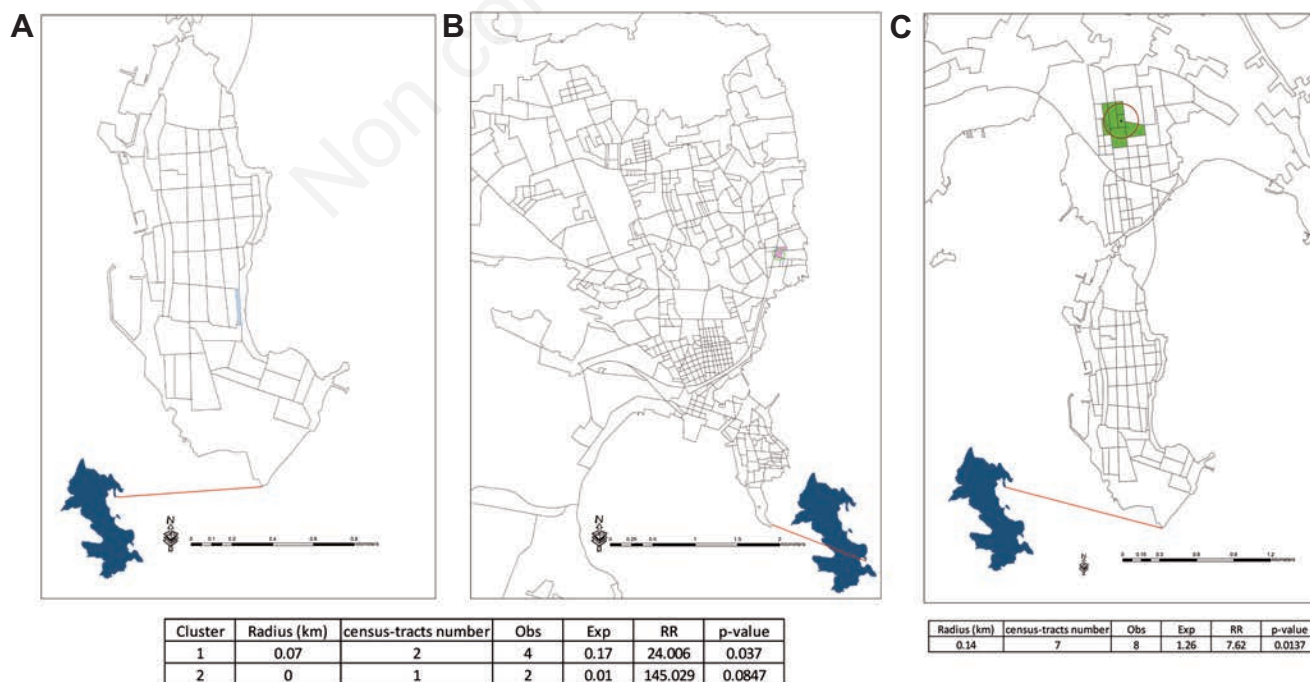| Neoplasms	Augusta Men Obs	SIR (95%CI)	Augusta Women Obs	SIR (95%CI)	Melilli Men Obs	SIR (95%CI)	Melilli Women Obs	SIR (95%CI)	Priolo Men Obs	SIR (95%CI)	Priolo Women Obs	SIR (95%CI)	Syracuse Men Obs	SIR (95%CI)	Syracuse Women Obs	SIR (95%CI)
All malignant neoplasms	687	1.21 (1.12-1.31)	570	1.25 (1.15-1.36)	187	1.02 (0.88-1.18)	139	1.00 (0.84-1.18)	206	1.24 (1.08-1.43)	129	0.94 (0.79-1.12)	2,346	1.21 (1.16-1.26)	1,894	1.14 (1.09-1.19)
Oesophagus	4	1.05 (0.28-2.67)	3	2.08 (0.43-6.07)	1	0.85 (0.02-4.73)	0		0		1	2.75 (0.07-15)	11	0.86 (0.43-1.53)	1	0.19 (0-1.08)
Stomach	25	0.96 (0.62-1.42)	8	0.62 (0.27-1.21)	8	0.96 (0.41-1.89)	5	1.37 (0.44-3.19)	10	1.36 (0.65-2.50)	5	1.43 (0.46-3.33)	65	0.73 (0.57-0.93)	41	0.88 (0.63-1.20)
Colon-rectum	90	1.26 (1.01-1.55)	81	1.23 (0.98-1.53)	18	0.79 (0.47-1.25)	18	0.94 (0.56-1.49)	28	1.37 (0.91-1.98)	19	1.01 (0.61-1.58)	286	1.18 (1.04-1.32)	242	1.01 (0.89-1.15)
Liver	39	1.30 (0.92-1.77)	27	1.99 (1.31-2.89)	10	1.03 (0.49-1.90)	7	1.84 (0.74-3.80)	9	1.03 (0.47-1.95)	4	1.05 (0.29-2.69)	109	1.05 (0.86-1.27)	57	1.16 (0.88-1.51)
Gallbladder and biliary tract	13	1.64 (0.87-2.81)	10	0.91 (0.44-1.67)	0		5	1.58 (0.51-3.69)	2	0.90 (0.11-3.27)	2	0.64 (0.08-2.30)	31	1.17 (0.79-1.66)	52	1.29 (0.97-1.70)
Pancreas	21	1.31 (0.81-2.00)	18	1.27 (0.75-2.00)	6	1.18 (0.43-2.56)	10	2.52 (1.21-4.64)	6	1.33 (0.49-2.90)	5	1.26 (0.41-2.94)	75	1.37 (1.08-1.72)	74	1.44 (1.13-1.81)
Larynx	16	1.33 (0.76-2.16)	0		5	1.26 (0.41-2.95)	0		4	1.09 (0.30-2.79)	0		66	1.58 (1.22-2.01)	1	0.20 (0-1.09)
Trachea, bronchus and lung	123	1.25 (1.04-1.50)	23	1.37 (0.87-2.05)	34	1.07 (0.74-1.50)	2	0.38 (0.05-1.37)	32	1.12 (0.76-1.57)	3	0.59 (0.12-1.72)	420	1.25 (1.13-1.37)	81	1.32 (1.04-1.63)
Mesothelioma of pleura	14	4.21 (2.30-7.06)	4	5.12 (1.39-13.00)	4	3.63 (0.99-9.29)	0		3	3.04 (0.63-8.88)	1	4.59 (0.12-26)	17	1.46 (0.85-2.34)	4	1.40 (0.38-3.58)
Connective and soft tissue	2	0.44 (0.05-1.58)	1	0.29 (0-1.61)	2	1.29 (0.16-4.66)	1	0.93 (0.02-5.19)	2	1.36 (0.16-4.91)	1	0.98 (0.01-5.44)	12	0.76 (0.39-1.32)	10	0.79 (0.38-1.46)
Melanoma of skin	13	1.45 (0.77-2.48)	17	2.66 (1.55-4.25)	3	1.00 (0.21-2.93)	5	2.44 (0.79-5.69)	2	0.72 (0.09-2.58)	2	1.02 (0.12-3.67)	46	1.47 (1.08-1.97)	42	1.80 (1.30-2.44)
Bone	1	0.55 (0.01-3.03)	1	1.25 (0.03-6.98)	0		0		2	2.95 (0.36-11)	0		6	0.90 (0.33-1.96)	5	1.73 (0.56-4.03)
Breast	1	0.77 (0.02-4.29)	174	1.30 (1.12-1.51)	0		40	0.95 (0.68-1.29)	1	2.62 (0.07-15)	39	0.94 (0.67-1.29)	11	2.50 (1.25-4.47)	561	1.14 (1.05-1.24)
Uterus			36	0.79 (0.55-1.09)			14	1.00 (0.54-1.67)			13	0.93 (0.50-1.60)			153	0.91 (0.77-1.07)
Cervix of uterus			6	0.49 (0.18-1.06)			3	0.75 (0.15-2.18)			2	0.51 (0.06-1.85)			40	0.87 (0.62-1.19)
Corpus of uterus			30	0.90 (0.61-1.29)			11	1.10 (0.55-1.96)			11	1.10 (0.55-1.96)			113	0.92 (0.76-1.11)
Ovary			20	1.15 (0.70-1.78)			3	0.54 (0.11-1.59)			4	0.74 (0.20-1.89)			70	1.09 (0.85-1.38)
Prostate	88	1.08 (0.86-1.33)			27	1.06 (0.70-1.55)			37	1.63 (1.15-2.25)			342	1.25 (1.12-1.39)		
Testis	6	1.04 (0.38-2.25)			2	0.89 (0.11-3.21)			2	0.94 (0.11-3.41)			34	1.61 (1.11-2.24)		

Continued on next page.

Table 4. Continued from previous page.

Neoplasms	Augusta Men Obs	Augusta Men SIR (95%CI)	Augusta Women Obs	Augusta Women SIR (95%CI)	Melilli Men Obs	Melilli Men SIR (95%CI)	Melilli Women Obs	Melilli Women SIR (95%CI)	Priolo Men Obs	Priolo Men SIR (95%CI)	Priolo Women Obs	Priolo Women SIR (95%CI)	Syracuse Men Obs	Syracuse Men SIR (95%CI)	Syracuse Women Obs	Syracuse Women SIR (95%CI)
Bladder	94	1.14 (0.92-1.40)	14	1.35 (0.74-2.26)	31	1.18 (0.80-1.68)	4	1.34 (0.36-3.43)	26	1.10 (0.72-1.61)	3	1.03 (0.21-3.01)	339	1.21 (1.08-1.34)	63	1.69 (1.30-2.16)
Kidney and other urinary organs	19	1.47 (0.88-2.29)	6	1.05 (0.39-2.29)	7	1.59 (0.64-3.28)	1	0.58 (0.01-3.23)	3	0.75 (0.16-2.20)	1	0.58 (0.01-3.22)	58	1.27 (0.97-1.64)	31	1.50 (1.02-2.13)
Central nervous system	22	2.15 (1.35-3.25)	13	1.48 (0.79-2.54)	3	0.88 (0.18-2.57)	2	0.75 (0.09-2.72)	4	1.27 (0.35-3.26)	1	0.39 (0.01-2.16)	50	1.42 (1.05-1.87)	31	0.97 (0.66-1.38)
Thyroid gland	10	1.78 (0.85-3.27)	39	1.65 (1.17-2.25)	1	0.47 (0.01-2.61)	3	0.36 (0.07-1.04)	2	1.00 (0.21-3.62)	4	0.49 (0.13-1.25)	26	1.26 (0.82-1.84)	105	1.18 (0.96-1.43)
Lymphohemopoietic system	47	0.92 (0.67-1.22)	45	1.20 (0.88-1.61)	10	0.58 (0.28-1.06)	11	0.94 (0.47-1.69)	20	1.25 (0.76-1.93)	13	1.15 (0.61-1.97)	224	1.26 (1.10-1.43)	144	1.06 (0.89-1.25)
Non-Hodgkin lymphomas	16	0.79 (0.45-1.29)	20	1.27 (0.77-1.95)	5	0.73 (0.24-1.70)	5	0.99 (0.32-2.32)	4	0.63 (0.17-1.61)	5	1.02 (0.33-2.38)	89	1.26 (1.01-1.55)	57	0.98 (0.74-1.27)
Hodgkin lymphoma	6	1.65 (0.61-3.60)	5	1.59 (0.52-3.72)	0		3	2.60 (0.54-7.60)	4	3.16 (0.86-8.08)	3	2.85 (0.59-8.32)	16	1.24 (0.71-2.01)	12	1.04 (0.54-1.82)
Myeloma	10	1.03 (0.49-1.88)	5	0.73 (0.24-1.70)	3	0.96 (0.20-2.79)	2	1.03 (0.12-3.72)	4	1.43 (0.39-3.65)	4	2.11 (0.58-5.41)	38	1.13 (0.80-1.55)	33	1.33 (0.92-1.87)
Leukaemias	15	0.84 (0.47-1.39)	15	1.29 (0.72-2.13)	2	0.34 (0.04-1.22)	1	0.28 (0.01-1.57)	8	1.44 (0.62-2.83)	1	0.29 (0.01-1.61)	81	1.33 (1.05-1.65)	42	1.00 (0.72-1.36)
Lymphoid leukaemias	4	0.64 (0.17-1.63)	3	0.62 (0.13-1.80)	1	0.46 (0.01-2.59)	0		4	1.94 (0.53-4.98)	1	0.71 (0.02-3.96)	39	1.81 (1.28-2.47)	20	1.15 (0.70-1.77)
Acute lymphoblastic leukaemia	2	0.76 (0.09-2.76)	1	0.64 (0.02-3.54)	0		0		1	0.96 (0.02-5.33)	0		10	1.07 (0.51-1.97)	9	1.56 (0.71-2.96)
Chronic lymphocitic leukaemia	2	0.55 (0.07-1.98)	2	0.61 (0.07-2.20)	1	0.89 (0.02-4.97)	0		3	2.96 (0.61-8.65)	1	1.20 (0.03-6.69)	29	2.37 (1.59-3.40)	11	0.94 (0.47-1.69)
Myeloid leukaemias	10	1.32 (0.63-2.43)	7	1.77 (0.71-3.65)	1	0.41 (0.01-2.28)	0		3	1.30 (0.27-3.79)	0		29	1.12 (0.75-1.60)	17	1.18 (0.69-1.89)
Acute myeloblastic leukaemia	6	1.28 (0.47-2.79)	5	1.95 (0.63-4.55)	0		0		1	0.70 (0.02-3.92)	0		17	1.06 (0.62-1.70)	9	0.96 (0.44-1.82)
Chronic myeloid leukaemia	4	1.38 (0.38-3.54)	2	1.44 (0.17-5.20)	1	1.08 (0.03-6.04)	0		2	2.25 (0.27-8.12)	0		12	1.21 (0.62-2.11)	8	1.60 (0.69-3.16)

Obs, observed cases; SIR, standardised incidence ratio; 95%CI, 95% confidence interval.

a large number of environmental chemicals are suspected of playing a role in breast cancer, in addition to hormone-related risk factors. Breast cancer is associated with sufficient evidence with exposure to alcoholic beverages, estrogen-progestogen therapies and diethylstilbestrol, X rays and gamma radiations (IARC, 2014a); limited evidence has been found for the association with digoxin, estrogen menopausal therapy, shift work that involves circadian disruption, tobacco smoking and exposure to ethylene oxide and PCBs (IARC, 2014a). The European case-control study on occupational exposure to endocrine disrupting chemicals in male breast cancer pointed out the increased incidence of male breast cancer with a possible role of occupational exposures to petrol and petroleum solvents in motor vehicle mechanics and, moreover, of occupational exposure to endocrine disrupting chemicals such as alkylphenolic compounds (Villeneuve *et al.*, 2010). Cancers of the lung, bladder, breast, skin melanoma and pleural mesothelioma found in excess among both males and females deserve specific concern in view of *a priori* evidence of association with exposure to PICs present in the area for the first four, and of the presence of potential asbestos sources for the latter.

Syracuse and, partially, Augusta municipality contributed to the findings concerning the CS overall area. The absence of observed excesses in Priolo and Melilli should not be overlooked, because of the low statistical power due to small population size. The results of clustering with the inclusion of Syracuse, detecting significant clusters of lung and non-Hodgkin lymphoma in a specific sub-area in this town, may be partly explained by different levels of air pollution exposure; the larger population size (with respect to the other municipalities of the CS) might have influenced the analysis. The lack of clustering at the census-tract level for some diseases found in excess at municipal level may be due to several factors: role of exposure pathways not related to spatial distribution of environmental contamination (*e.g.* drinking water, diet) and individual risk factors (occupational setting, socioeconomic status), and also to chance findings due to the low population size of each census-tract considered as the geographic unit in the cluster analysis. Nevertheless, some tumours (lung, thyroid, pancreas) produce clusters in populated sub-areas that seem to be affected by industrial air pollutants.

Conclusions

The present study contributes to the assessment of the spatial distribution of cancer diseases in the population living in the Priolo CS, Sicily. Etiological hypotheses on the links between the occurrence of a number of carcinogenic agents and the observed increased incidence of some cancer sites were generated. The results confirm a health status of the population living in Priolo CS that is worse than the Province of Syracuse taken as a whole, for which environmental exposure might play a role. Environmental remediation, currently in progress, should be accelerated together with an updating of the regulation of the industrial emissions. The establishment of an accurate environmental monitoring system integrated with a health surveillance plan is warranted.

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