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Ecological studies of cancer incidence in an area interested by dumping waste sites in Campania (Italy)

Lucia Fazzo[a], Marco De Santis[a], Francesco Mitis[b], Marta Benedetti[a], Marco Martuzzi[b], Pietro Comba[a] and Mario Fusco[c]

[a] *Dipartimento di Ambiente e Connessa Prevenzione Primaria, Istituto Superiore di Sanità, Rome, Italy*
[b] *World Health Organization, Centro Europeo Ambiente e Salute, Rome, Italy*
[c] *Registro Tumori della Regione Campania c/o ASL Napoli 4, Brusciano, Italy*

Summary. Cancer incidence was investigated in an area which has been affected by the illegal practices of dumping hazardous waste and setting fire to mismanaged waste. For the 35 municipalities of this area that are served by a Cancer Registry, municipal standardized incidence ratios (SIR) and hierarchical Bayesian estimators (BIR) were computed. Moreover, municipal spatial clustering and a Poisson regression by municipality index of waste-related exposure were performed for 10 cancer types. Increased municipality SIRs were found for some cancer types. The BIRs confirmed the increases for liver cancer in two municipalities. Statistically significant clusters were detected for liver, lung, leukaemia and soft tissue sarcomas. In the regression analysis, testis cancer showed significant trend with the index of waste-related exposure (RR = 1.18).

Key words: cancer incidence, waste dumping sites, testicular neoplasms, liver neoplasms.

Riassunto *(Studi ecologici dell'incidenza tumorale in un'area interessata da siti di smaltimento di rifiuti in Campania, Italia)*. È stata investigata l'incidenza oncologica in un'area interessata da pratiche illegali di smaltimento e di combustione incontrollata di rifiuti. Per i 35 comuni di quest'area serviti da un Registro Tumori sono stati calcolati i rapporti standardizzati di incidenza (*standardized incidence ratios,* SIR) e gli stimatori bayesiani (BIR). Per 10 sedi tumorali sono state eseguite, inoltre, analisi di cluster spaziali e di regressione con un indice municipale di esposizione a rifiuti. SIR in eccesso sono stati osservati per diverse sedi tumorali; i BIR hanno confermato gli eccessi di tumore epatico in due comuni. I tumori epatici e polmonari, le leucemie e i sarcomi dei tessuti molli hanno mostrato cluster significativi. Nell'analisi di regressione il tumore del testicolo ha mostrato un trend in eccesso significativo (RR = 1,18).

Parole chiave: incidenza tumorale, rifiuti, neoplasie del testicolo, neoplasie del fegato.

INTRODUCTION

The territory of Naples and Caserta Provinces in Campania Region (Southern Italy), consisting of 196 municipalities, has been extensively affected, since the eighties, by the illegal practices of dumping hazardous waste and setting fire to both hazardous and solid urban mismanaged waste. A part of this area (77 municipalities) has been declared "site of national interest for remediation" by the Ministry of Environment, because of the presence of dumping waste sites, together with other sources of environmental pollution.

In the last decades, several studies on the possible health impact of waste management and disposal were published. A WHO Report on these issues was published in 2007; it concluded that the scientific literature provides some indication of the association between residence near a landfill site and adverse health effects, even though the evidence (stronger for reproductive outcomes than for cancer) is not conclusive. Similar conclusions were reached for incinerators, with specific reference to a possible role of dioxins in the increased risk in soft tissue sarcomas (STS) and non-Hodgkin's lymphoma (NHL) [1]. A more recent review of epidemiological studies published between 1983 and 2008 about health effects of solid urban waste management reached comparable conclusions [2].

For some cancer types *a priori* hypotheses of an association with residence near waste management sites appear to be more consistent, even if with the limitations indicated by the above-mentioned reviews. Associations with residence in the neighbourhood of landfill sites have been suggested for following cancer types: liver, lung, stomach, kidney, bladder and leukaemia [3-9].

Address for correspondence: Lucia Fazzo, Dipartimento di Ambiente e Connessa Prevenzione Primaria, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: lucia.fazzo@iss.it.

In light of the widespread practice of setting fire to waste deposits in parts of the study area and the subsequent detection of high levels of dioxins in animal milk [10], even if no waste incinerator was operating in the area, literature about the health impact of incinerators was considered. Increased risks for liver and lung cancer, NHL and STS were reported in the neighbourhood of incinerators [2].

Even if there is not direct epidemiological evidence of an increase risk of testis cancer in areas with waste dumping sites, testis cancer was included in the study. The *a priori* etiological hypotheses were derived by awareness of the possible etiological role of exposure to endocrine disruptors [11]. The endocrine disruptors are also taken into account in the etiology of congenital malformations [12] and in the assessment of congenital malformations risk around landfills [1]. Similarly, biliary tract cancer was included for its suspected association with exposure to endocrine disruptors [13].

With regard to the territory of Naples and Caserta provinces, since 2006 several studies have been carried out on cause-specific mortality and prevalence of congenital malformations in this area, in order to investigate the health status of the population and its potential relationship with the presence of dumping waste sites. The first study showed increased risks in cancer mortality in the southern part of Caserta province and in the northern part of Naples province [14]. Subsequently, municipal cluster analysis of cancer mortality and congenital malformations occurrence showed significant clusters of municipalities located in the same areas evidenced in the previous study [15]. More recently, a study has been published on the correlation between cancer mortality, prevalence of congenital anomalies at birth and a municipal waste-related exposure index [16]. The findings, adjusted for socioeconomic deprivation, show statistically significant increased relative risks in high exposure compared to low exposure index municipalities for all causes, all cancer and liver cancer mortality in both genders, stomach cancer and lung cancer in men, and for the occurrence of congenital anomalies of the internal urogenital tract and of the central nervous system.

The aim of the present study is to describe the spatial distribution of neoplastic disease incidence in this area and to generate hypotheses of etiological interest with respect to the aforementioned waste-related exposures, that might subsequently be tested by *ad hoc* analytical studies. Cancer incidence is in fact a more valid outcome than mortality, because it is based on pathology data and it is not affected by differential survival patterns reflecting differences in access to appropriate diagnostic and therapeutic procedures. Furthermore, the use of incidence data enables the study of neoplastic diseases characterized by low mortality rates. The present study was prompted by the availability of cancer incidence data in a subarea of the Province of Naples, comprising 35 municipalities, that is served by a cancer registry *(Figure 1)*.

MATERIALS AND METHODS

The study area is constituted by the municipalities of Naples Province, served by a Cancer Registry; the time-window of analysis is from 1997 to 2005, corresponding to that of the Registry's time coverage.

The Cancer Registry of Local Health Authority "Naples 4", the only cancer registry operating in Caserta and Naples Provinces, constituted the source of the study subjects. The Registry is part of the Italian Network of Cancer Registries (AIRTUM) and is certified by International Agency for Research on Cancer (IARC) at the international level [17].

The Cancer Registry database includes 17 300 cases of cancer diagnosed in the period 1997-2005 and

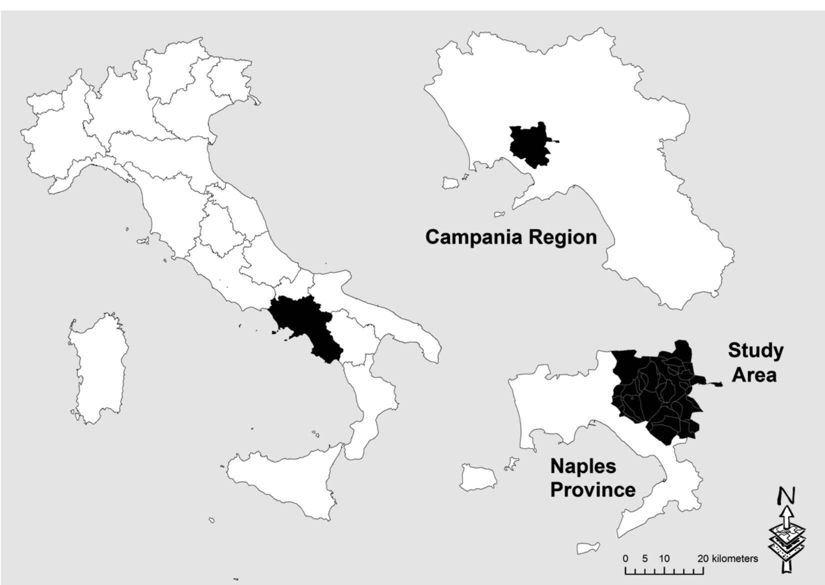


Fig. 1 | *The map of study area of Naples Province in Campania Region (Italy).*

resident at the time of diagnosis in the 35 municipalities of area of the Local Health Authority "Naples 4". According to the coding rules adopted in cancer registration, International Classification Diseases for Oncology 3rd edition (ICD-O-3) codes based on topographic criteria were used. The SIR and BIR analyses included 14 892 cases diagnosed in the period 1997-2005 with the following 25 cancer types: head and neck, esophagus, stomach, colon-rectum, liver, biliary ducts, pancreas, larynx, lung, skin (melanoma), mesothelioma, breast, uterine cervix, uterus, prostate, testis, kidney, bladder, brain, thyroid, Hodgkin's lymphoma, non Hodgkin's lymphoma, myeloma, leukaemia and malignant tumours of the connective and soft tissue (the category of the topographical classification in which most of the soft-tissue sarcomas are included); analyses were also performed for all cancers (17 300 cases) and all cancers excluding skin (16 156 cases).

Given the specific interest of investigating soft-tissue sarcomas (STS), that have been associated with exposure to dioxins [18], possibly released by uncontrolled combustions, an additional analysis based on morphological classification was performed. This analysis was possible because all cancer cases considered by the Registry were diagnosed by pathology laboratories and histological examinations of primary tumour were available; subsequently Cancer Registry experts checked each report with respect to compliance with morphological classification in ICD 10th revision code. For adult STS (age > 19 years), histologically-confirmed first-incident STS cases, originating in non-visceral and visceral locations, were enrolled in the study. Inclusion criteria were based on the histological classification of soft tissue tumours of Weiss & Goldblum (2007) [19], very similar to the WHO classification (2002) [20]. Kaposi's sarcoma were excluded. For childhood (age 0-14 years) and adolescent (age 15-19 years) STS cases were those with a first-incident histologically confirmed diagnosis of malignant STS, originating in non-visceral and visceral locations. We selected all malignant types included in the IX site group (soft tissue and other extraosseous sarcomas) of the third edition of the International Classification of Childhood Cancer (ICCC-3), excluding benign/intermediate types and Kaposi sarcoma.

The total resident population in the study area is constituted by 538 243 people (at 2001 census), on a surface of 425 kmq. The most populated municipality includes 47 940 inhabitants and the smallest 1769 subjects (at 2001 census). For each municipality, a database of cases specific by cancer type, gender and age (five-year classes) was prepared.

Standardized incidence ratios (SIRs) and hierarchical Bayesian estimators (BIRs) were computed for each municipality, using the whole population of the 35 municipalities area as reference. SIRs with their 95% confidence intervals were computed using the quadratic approximation to the Poisson log-likelihood for the log rate parameters, in STATA software package. BIRs, bayesian smoothed relative risks, with their 95% credibility intervals were computed with the Rapid Inquiry Facility (RIF), using WinBugs [21, 22] based on the procedures by Besag *et al,* [23]. For STS morphologic classification only, 90% confidence intervals were used, in order to balance the fairly low statistical power due to small sample, also in view of the relatively stronger available *a priori* hypotheses.

Clustering and regression analyses were performed only for 10 of all the 25 selected cancer types, for which *a priori* hypotheses of an association with residence near waste dumping sites were available (stomach, liver, biliary ducts, lung, soft-tissue sarcomas, kidney, bladder, non Hodgkin's lymphoma, leukaemia, testis) and for all cancers. The selection of these cancer types was based on the examination of abovementioned systematic reviews and other recent sources [1, 24, 2].

Cluster analysis was performed in order to investigate spatial aggregation of cases resident in neighbouring municipalities in the whole study area. Municipal spatial cluster of cases were identified by using SatScan software (version 6) assuming a Poisson model for the distribution of cases in each municipality. The adopted procedure spatial scan statistics [25] employs a circular window whose radius was fixed with a maximum of 10 km and was centred at each step on one municipality identified by x, y coordinates of its townhall. We selected a significance threshold of $p < 0.10$. The underlying etiological hypothesis was that of a diffuse air, soil and water contamination in some subareas of the territory included in the study.

Clustering analysis took into account socioeconomic status. We calculated municipal deprivation index (DI) based on five 1991 census variables (education, unemployment, housing ownership, surface of the dwelling and family structure) [26]. The municipalities were subdivided in quintiles with respect to the value of deprivation index in the study area (1 = least deprived; 5 = most deprived); the value of DI quintile of each municipality is used in the analysis as covariate, and the findings are adjusted by DI. The use of DI by index classes rather than using the basic index is commonly endorsed in environmental epidemiology [27], and has previously been adopted in this study setting [15, 16].

In order to evaluate the possible association between cancer incidence and environmental exposure to waste dumping sites, we used Poisson regression method (in STATA software package) applying to each municipality a waste-related exposure index (WEI). The latter was built within the previous mortality study [16] and it is described in detail in a recent paper [28].

The WEI was constructed on the basis of a database of legal waste landfills and illegal dumping sites present in the region (years 1997-2003), created by the regional Environmental Protection Agency. Many of these sites have been present for at least two decades, and have not yet been cleaned up [29]. When the WEI was calculated, routinely environmental monitoring data in the area of interest were not geocoded. The municipal WEI took into account the potential hazard of each dumping waste site and the percentage of population resident in impact areas of the single waste site [28].

In order to use the index in regression analysis, municipalities were categorized in five groups of WEI, using the so-called natural breaks, that maximize homogeneity within groups and heterogeneity between groups (1 = least at risk; 5 = most at risk).

With regard to the area of the present study, 16.5% of it, comprising 5.5% of resident population (total population, at 2001 census: 29 434 people), is interested by waste impact areas. *Table 1* shows the number of impact areas, interested territory and population in each municipality. The distribution of 35 municipalities in the different classes of DI and WEI is shown in *Figure 2*. Only one municipality is in the fourth and fifth WEI classes respectively. This distribution creates some limitations in the computation of correlation coefficients, which was taken into account in the interpretation of findings. Poisson regression analyses to investigate WEI effects were adjusted by DI.

Table 1 | *Distribution of waste impact areas and resident population (at 2001 census) in impact areas, by municipality*

Municipality	no. impact areas	Total municipal area (km^2)	Area interested by impact areas (%)	Total resident population	Population resident in impact areas (%)
Acerra	70	54.44	33.3	45688	12.2
Brusciano	0	5.66	0.0	15309	0.0
Camposano	0	3.31	0.0	5303	0.0
Carbonara di Nola	4	3.63	47.6	2025	79.9
Casalnuovo di Napoli	4	7.77	2.8	47940	3.7
Casamarciano	10	6.35	27.4	3283	4.4
Castello di Cisterna	0	3.79	0.0	6716	0.0
Cercola	0	4.21	0.0	18876	0.0
Cicciano	1	7.29	8.7	12573	0.0
Cimitile	1	2.73	1.0	6840	0.0
Comiziano	3	2.44	19.5	1769	18.1
Liveri	4	2.70	42.8	1815	24.5
Mariglianella	0	3.25	0.0	6199	0.0
Marigliano	6	22.45	5.1	30083	0.3
Massa di Somma	9	3.06	45.2	5908	29.4
Nola	35	38.98	20.1	32730	2.7
Ottaviano	3	19.92	4.7	22670	0.1
Palma Campania	15	20.56	22.9	14613	4.2
Poggiomarino	3	13.13	5.4	19653	0.5
Pollena Trocchia	5	7.97	20.2	13326	9.0
Pomigliano d'Arco	12	11.70	8.8	40519	1.8
Roccarainola	4	28.18	7.4	7182	0.3
San Gennaro Vesuviano	38	6.98	66.9	10035	62.7
San Giuseppe Vesuviano	9	14.10	17.8	24531	2.8
San Paolo Bel Sito	0	2.93	0.0	3356	0.0
San Vitaliano	26	5.35	64.2	5562	44.9
Sant'Anastasia	9	18.66	11.6	28023	2.9
Saviano	7	13.80	8.5	14755	2.5
Scisciano	9	5.47	6.9	4881	10.3
Somma Vesuviana	5	30.49	9.5	33261	0.2
Striano	1	7.61	0.0	7507	0.0
Terzigno	5	23.38	16.2	15870	3.5
Tufino	28	5.18	66.7	3247	73.4
Visciano	0	10.84	0.0	4621	0.0
Volla	0	6.17	0.0	21574	0.0

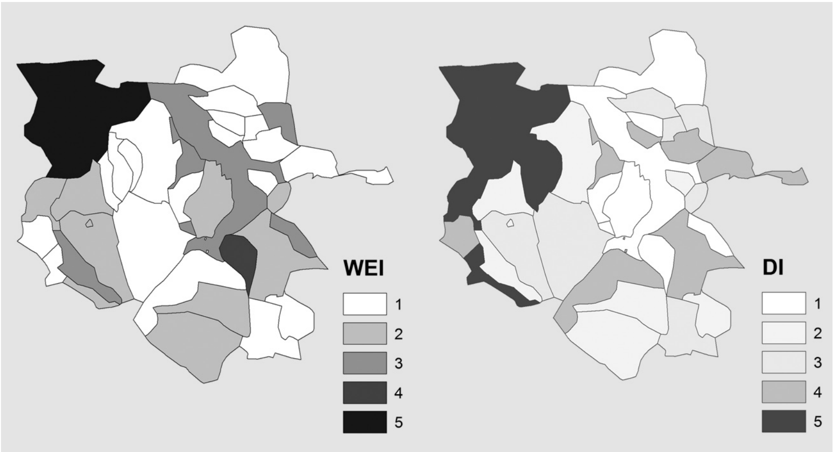


Fig. 2 | *Municipality distribution of Deprivation Index (DI) values subdivided in quintiles (1 = least deprived; 5 = most deprived) and of Waste Exposure Index (WEI) classes (1 = least at risk; 5 = most at risk).*

RESULTS

The annual average population and total cases for cancer types in the 1997-2005 period, by gender and by classes of deprivation index and waste exposure index are shown in *Table 2*.

SIR and BIR

Table 3 shows the number of municipalities where SIRs showed 95% confidence interval lower limit superior than 1. Only for morphologically classified soft-tissue sarcomas, we used 90% confidence interval.

Significantly increased SIRs were found for liver and lung cancer, non Hodgkin's lymphoma (NHL) and total leukaemia (ICD 10 rev: C91-95, including NAS leukaemia), in both genders separately; testis, esophagus, larynx, pancreas, thyroid gland cancer and morphologic soft-tissue sarcomas in men; stomach and topographic soft tissue sarcomas in the overall population; kidney, biliary ducts, brain cancer and myeloma in women. Only the increases for liver cancer were confirmed in two municipalities by BIRs with 95% credibility intervals lower limit superior than 1 (observed cases: 112, BIR = 1.41, 95% CrI = 1.17-1.68; observed cases: 100, BIR = 1.57; 95% CrI = 1.28-1.89) (findings not shown).

Clustering

Statistically significant clusters were detected in the total population for liver cancer (observed cases: 191, RR = 1.64, p-value = 0.0003; observed cases: 73, RR = 1.70, p-value = 0.0027), lung cancer (observed cases: 737, RR = 1.15, p-value = 0.08), total leukaemia (observed cases: 197, RR = 1.33, p-value = 0.05) and topographic soft tissue sarcomas (observed cases: 49, RR = 2.02, p-value = 0.08) *(Figures 3-6)*. Statistically significant clusters were detected for liver cancer also among men and women separately: two clusters among men (observed cases: 127, RR = 1.64, p-value = 0.0007; observed cases: 62, RR = 1.60, p-value = 0.0470, respectively) and one cluster in women (observed cases: 63, RR = 1.684, p-value = 0.0213) (data not shown).

The two significant clusters detected for liver cancer in the total population substantially correspond to those detected among men; one of them is significant also among women. These clusters are located in the northern part of the study area, but they are not contiguous.

The leukaemia cluster included one municipality in the WEI 4th category; the only municipality of the WEI 5th category was not included in any cluster.

Other cancer types didn't show significant clusters among two genders separately.

Regression

The findings of correlation analysis are shown in *Table 4*.

Relative risks of each WEI group with respect to the first WEI group are reported. The linear risk trends across the five WEI groups are also shown. The results with 95% CI lower limit > 1 are reported in bold.

Only testis cancer incidence showed a statistically significant increasing trend with the WEI categories (RR = 1.18; 95% CI: 1.03-1.35).

Significantly increased relative risks for some cancer types occurred in specific WEI categories, with respect to the first class, used as reference: for lung cancer (RR = 1.44; 1.01-2.05) and bladder cancer (RR = 1.85; 1.13-3.03) in the fourth class and for the latter cancer type also in the second class (RR = 1.19; 1.01-1.41) in men; biliary ducts cancer in the third class (RR = 1.63; 1.00-2.63) and leukaemia in the fifth class (RR = 1.82; 1.08-3.07) in women. In women, the relative risk for liver cancer was found significantly decreased (RR = 0.68; 0.53-0.86) in the second class.

DISCUSSION

The study findings warrant some comments.

Liver cancer showed a significant increase in risk in terms of SIR, BIR and cluster analysis in a group of municipalities located in the northern part of the study area. Three of them also showed significantly

Table 2 | *Population and cancer cases (1997-2005), by gender, DI (quintiles) and WEI category*

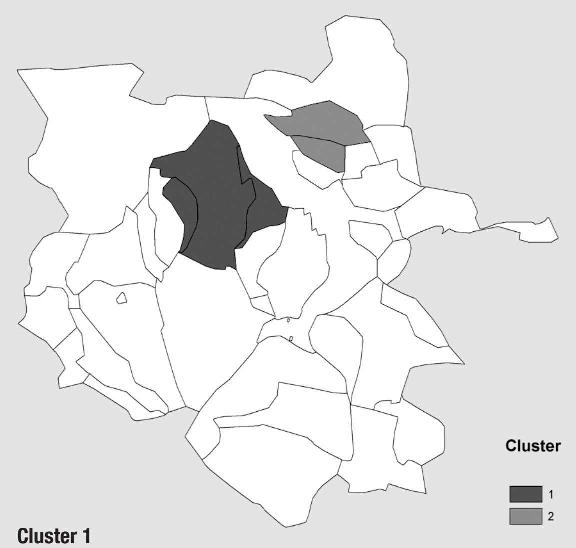
Males Waste index	Municipalities	Annual average population	All cancers	Stomach	Liver	Biliary ducts	Lung	STS (topographic)	STS (morphologic)	Kidney	Bladder	NHL	Leukaemia	Testis
I group	19	114312	4102	187	452	43	799	21	30	76	319	163	159	45
II group	9	95798	3353	135	293	39	680	24	32	66	293	109	135	44
III group	5	27887	1065	38	97	12	217	1	7	21	100	38	32	17
IV group	1	4854	169	10	19	4	39	0	2	2	21	2	6	0
V group	1	22535	802	34	112	9	146	1	3	12	56	25	28	19
Total	35	265386	9491	404	973	107	1881	47	74	177	789	337	360	125
Females **Waste index**	**Municipalities**	**Annual average population**	**All cancers**	**Stomach**	**Liver**	**Biliary ducts**	**Lung**	**STS (topographic)**	**STS (morphologic)**	**Kidney**	**Bladder**	**NHL**	**Leukaemia**	**Testis**
I group	19	118078	3352	114	191	85	147	14	34	62	35	133	108	0
II group	9	99329	2747	102	116	56	136	14	29	52	44	121	106	0
III group	5	29387	937	36	47	34	40	1	6	19	17	50	30	0
IV group	1	5057	136	5	8	2	7	0	0	0	3	8	3	0
V group	1	22977	637	26	41	14	26	3	5	12	6	30	28	0
Total	35	274827	7809	283	403	191	356	32	74	145	105	342	275	0
Males **Deprivation index**	**Municipalities**	**Annual average population**	**All cancers**	**Stomach**	**Liver**	**Biliary ducts**	**Lung**	**STS (topographic)**	**STS (morphologic)**	**Kidney**	**Bladder**	**NHL**	**Leukaemia**	**Testis**
I group	5	37581	1429	61	122	18	278	5	15	28	132	46	44	17
II group	5	66803	2528	123	275	34	510	15	23	45	192	85	80	29
III group	5	49600	1771	73	156	14	376	9	12	29	153	57	83	24
IV group	5	39388	1443	61	139	18	279	7	11	35	126	60	52	19
V group	5	72014	2320	86	281	23	438	11	13	40	186	89	101	36
Total	35	265386	9491	404	973	107	1881	47	74	177	789	337	360	125
Females **Deprivation index**	**Municipalities**	**Annual average population**	**All cancers**	**Stomach**	**Liver**	**Biliary ducts**	**Lung**	**STS (topographic)**	**STS (morphologic)**	**Kidney**	**Bladder**	**NHL**	**Leukaemia**	**Testis**
I group	5	39569	1241	49	68	33	51	3	5	20	20	62	33	0
II group	5	70227	2085	83	115	49	83	6	22	35	33	97	88	0
III group	5	50862	1446	55	66	42	69	7	15	27	20	57	56	0
IV group	5	40534	1153	36	50	29	58	5	13	28	14	45	36	0
V group	5	73635	1884	60	104	38	95	11	19	35	18	81	62	0
Total	35	274827	7809	283	403	191	356	32	74	145	105	342	275	0

Table 3 | *Number of municipal Standardized Incidence Ratios (SIR) with 95% CI lower limit > 1, by cancer type*

Cancer type	ICD 10 rev	no. SIR Men	Women	Overall
Stomach	C16	0	0	2
Liver	C22	3	2	4
Lung	C33-34	1	1	2
Connective and soft tissue	C49	0	0	1
STS morphologic*		1	0	0
Kidney	C64	0	1	1
Bladder	C67	0	0	0
NHL	C82-85. C96	1	1	2
Leukaemia	C91-95	2	1	2
Testis	C62	1	-	-
Biliary ducts	C23-24	0	2	0
Esophagus	C15	1	0	1
Larynx	C32	2	0	1
Pancreas	C25	1	0	1
Brain	C71	0	1	1
Thyroid gland	C73	1	0	1
Myeloma	C88-90	0	1	0

** for morphologic STS: 90% CI*

increased mortality from liver cancer in the previous study [16]. In the regression analysis, a positive trend across the five WEI groups was found, but statistical significance was not reached, while it had been obtained in the mortality analysis. Liver cancer is a multifactorial disease, whose most important etiological factor is infection by B and C hepatitis virus, which has been shown to be endemic in the area [30], but does not seem to completely explain the geographic distribution of liver cancer incidence. Alcohol consumption is also a well ascertained risk



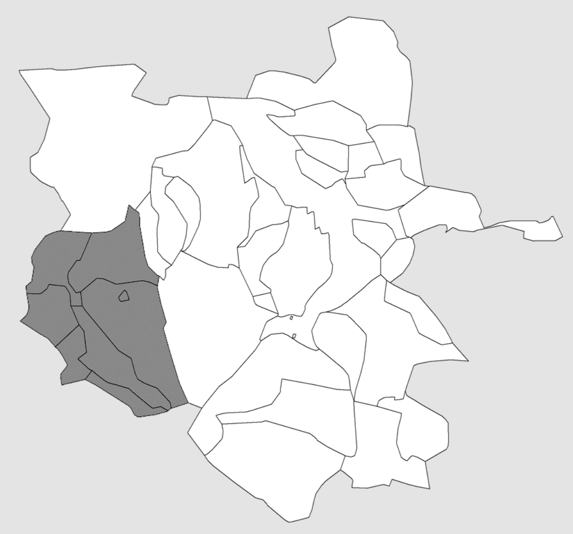
Cluster 1

Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	*p*-value
Marigliano	3	2.18	191	123.15	1.64	0.0003

Cluster 2

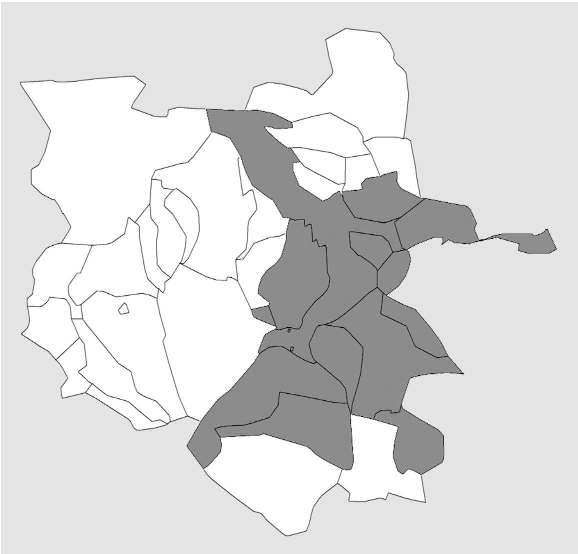
Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	*p*-value
Camposano	2	1.03	73	43.90	1.70	0.0027

Fig. 3 | *Statistically significant clusters for liver cancer incidence, total population.*



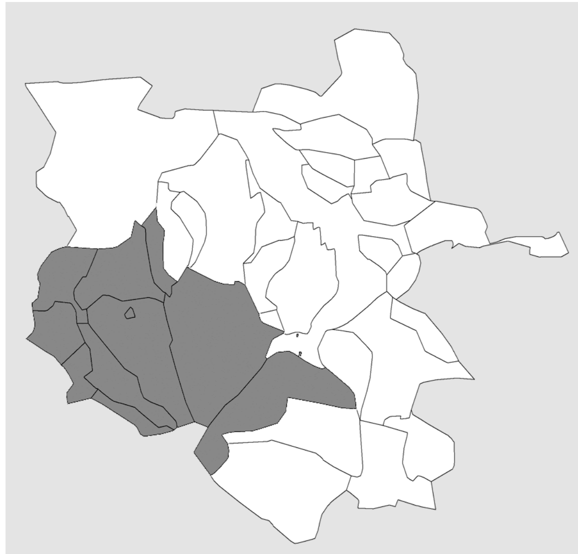
Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	*p*-value
Cercola	7	6.18	737	668.12	1.15	0.0843

Fig. 4 | *Statistically significant cluster for lung cancer incidence, total population.*



Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	*p*-value
Palma Campania	12	7.04	197	160.32	1.33	0.0537

Fig. 5 | *Statistically significant cluster for leukaemia incidence, total population.*



Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	*p*-value
Massa di Somma	10	8.36	49	35.32	2.02	0.0843

Fig. 6 | *Statistically significant cluster for soft-tissue sarcomas (topographic) incidence, total population.*

factor [31], while the role of socioeconomic conditions is controversial [32]. The possibility of an interaction between hepatitis virus and hepatotoxic agents in liver carcinogenesis has also been raised, in particular if these chemicals have a fibrogenic action, as vinyl chloride [33].

Taking into account the consistent *a priori* hypothesis of a possible association between liver cancer and waste disposal and the findings of the several studies in the area of interest, specific *ad hoc* studies in this area are warranted.

Two neighbouring municipalities showed significant results for SIR and clustering with regards to lung cancer, one of them also showed an increased incidence of pleural mesothelioma. Lung cancer showed a positive trend in males in correlation analysis, also if not statistically significant, while significance was reached in the mortality study in males. Lung cancer has a well known multifactorial etiology; in this case the presence of an asbestos cement factory in the town with excess incidence of both lung cancer and mesothelioma points to a causal role of occupational asbestos exposure [34].

A significant cluster of leukaemia in total population and a non significant correlation with WEI in women were detected; the latter was partly due to a significant IRR in the highest score WEI category. These findings reflect the role of chance or different constellations of risk factors in the two genders, in light of the multifactorial etiology of this disease.

The present study detected a significant cluster of soft-tissue sarcoma (topographic classification), in the absence of correlation with WEI. The lack of correlation with WEI, together with the observation that the STS cluster is located in an area with high prevalence of greenhouse floriculture, may rather point to an etiologic role of herbicides and fungicides [35, 36].

The finding of a positive correlation between the waste-related exposure index (WEI) and the incidence of testicular cancer deserves some comments. The possible etiologic role of environmental exposure to endocrine disruptors has been suggested in some review articles, taking into account the multifactorial etiology of this disease [37, 11, 38]. The suspected association between endocrine disruptors and testicular cancer may be viewed within the frame of the Testicular Dysgenesis Syndrome, whose underlying cause might reflect a hormonal imbalance due to environmental or life-style factors during early foetal development [39, 40]. The possibility of an etiological role of endocrine disruptors ingested with milk during puberty was also recently raised [41].

In the present study, one municipality showed a significantly increased incidence of testicular cancer (based on 19 cases; SIR = 1.75, 95% CI = 1.05-2.73), and it contributed to the results of the regression analysis since it corresponded to the highest score of the waste-related exposure index. In the previous study a significant increase of congenital malformations of urogenital tract was detected in the same municipality [15]. An *ad hoc* analytical study is required in order to evaluate a possible environmental etiology of testicular cancer in this area and a possible role of in utero exposure.

As mentioned in the Introduction section, the study area is characterized by a major problem of hazardous waste dumping, but also by the widespread practice of setting fire to both urban and hazardous waste. In this context, the *a priori* hypotheses of etiological interest have been derived from the available evidence concerning the possible health effects associated with residence in the neighbourhood of both landfills and incinerators. The complexity of the setting thus impairs full comparability of the findings of the present study with those of most previously published investigations.

Besides the comment of the study findings, some considerations about validity issues are required.

The data provided by the Cancer Registry have been extensively validated prior to their inclusion in the database endorsed by the International Agency for Research on Cancer [17].

Several methods of spatial analysis were applied. SIR analysis was characterized by high sensitivity and detected a number of significant increases of different cancer types. A subgroup of these signals was evidenced by cluster analysis, while BIR analysis was more specific and less sensitive with respect to both SIR and cluster analysis, since expected figures are computed based on the average values of contiguous municipalities.

Two main limitations affect the waste-related exposure index (WEI).

The first limitation derives from the inherent difficulty in the enumeration of the dumping sites distributed in the study area, often not authorized if not openly illegal; furthermore, the abovementioned illegal practice of setting fire to urban and hazardous waste has not been adequately monitored and mapped. Although the hazard characterization procedure of dumping sites has certainly been hampered by lack of information on the complex mix of chemicals released in the environment, still landfill density may be seen as an indirect indication of exposure to landfill emissions when a more detailed modelling is precluded [42]. The index was developed in order to be used at the municipality level, subsuming an ecological approach, and it cannot, thus, predict exposure at individual level.

The second limitation regards the difference between the context in which the WEI was developed

Table 4 | *Incidence rate ratio for cancer by WEI category and by gender, adjusted for DI*

		Relative risks by waste index group*					
Cancer types – men	**cases**	**I**	**II**	**III**	**IV**	**V**	**Trend**
All cancers	9491	1	1.002	1.024	1.085	1.054	1.014
Stomach	404	1	0.834	0.726	1.289	1.194	0.991
Liver	973	1	0.737	0.929	1.366	1.145	1.045
Lung	1881	1	1.056	1.139	**1.440**	1.012	1.014
Connective and soft tissue	47	1	1.342	0.166	– §	0.244	0.742
STS (morphologic)	92	1	1.136	0.810	1.312	0.715	0.949
Kidney	177	1	1.133	1.045	0.635	0.943	0.975
Bladder	789	1	**1.195**	1.301	**1.850**	0.918	1.030
NHL	337	1	0.813	0.954	0.323	0.736	0.929
Leukaemia	360	1	1.096	0.963	1.193	0.835	0.962
Testis	125	1	1.257	1.607	- §	**2.732**	**1.177**
Biliary ducts	107	1	1.047	1.016	2.385	1.266	1.074
Cancer types – women	**cases**	**I**	**II**	**III**	**IV**	**V**	**Trend**
All cancers	7809	1	0.990	1.042	0.991	1.039	1.013
Stomach	283	1	1.050	1.043	0.938	1.565	1.067
Liver	403	1	**0.676**	0.820	0.929	1.075	1.030
Lung	356	1	1.195	1.203	1.469	0.831	0.996
Connective and soft tissue	32	1	1.336	0.300	– §	0.915	0.918
STS (morphologic)	77	1	1.042	1.179	0.000	0.723	0.946
Kidney	145	1	1.104	1.283	– §	1.117	0.994
Bladder	105	1	1.517	1.788	2.221	1.211	1.093
NHL	342	1	1.058	1.338	1.376	1.244	1.091
Leukaemia	375	1	1.141	1.158	0.856	**1.821**	1.068
Biliary ducts	191	1	0.825	**1.626**	0.691	1.042	1.019

In bold statistically significant relative risks are reported.
**The first class is used as reference.*
§Non observed figures.

(196 municipalities encompassing two provinces) and the setting of the present study (35 municipalities located in a subarea of the Naples province). The five categories of the score were based on a "natural break" approach in the previous mortality study [16]. In the present incidence study, based on 35 municipalities, only two of them have been allocated, respectively, to the fourth and fifth WEI category, thus hampering the regression approach. The regression analysis was anyhow performed in order to foster comparability with the previous mortality study, but the smaller number of municipalities included in the present investigation, that affected contrastability between WEI categories, and the resulting lower statistical power, determined a modest consistency between the two correlation studies.

As far as control of confounding is concerned, we took into account the socio-economic status and the results of cluster and regression analyses were adjusted by the municipal Deprivation Index, but a residual effect cannot be ruled out. We did not consider other possible confounding factors, as occupational exposures, lifestyle, tobacco consumption, that operate at the individual level, since the present study adopted an ecological design.

The area at study is not very large (424.48 km^2) but it is densely populated (538 443 people, at 2001 census) and presents a variety of occupational settings, including chemical and metal industries, quarries and rural areas with intensive agricultural activity and greenhouse productions. The possible contribution of the resulting environmental contamination to the cancer burden in the area remains at the moment an open question.

The issue of multiple testing should also be addressed in this frame. There is general agreement on the risk of generating false-positive results in geographical analyses [43] and surveillance projects [44] because of multiple testing of a same null hypothesis. It should be stressed, though, that no irreversible decision follows the observation of a statistically significant increase of the incidence of a given cancer in a particular municipality; the study findings, as previously stated, are essentially used to select cancer types and locations for subsequent analytical investigations.

CONCLUSIONS

The present study adopted an ecological approach, that is not apt to conclusively corroborate or refute specific etiologic hypotheses. Still, the study, based on a validated cancer registry data-base and employing an appropriate set of methodological procedures for spatial analysis, detected several signals requiring an *ad hoc* analytical investigation.

In particular, the study findings suggested an association between the aforementioned waste-related exposure index and the incidence of testicular cancer, which might require investigation by an analytical study. Clusters of liver cancer, leukaemia and soft-tissue sarcomas were detected in the study area, but due to the absence of a clear association with the waste-related exposure index and to poor knowledge of locally relevant occupational exposures, it is difficult to draw conclusions regarding possible associations.

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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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