RASSEGNE E ARTICOLI

Residential proximity to an industrial incinerator and risk of soft-tissue sarcoma, 1999-2014

Rischio di sarcoma dei tessuti molli in residenti nelle vicinanze di un inceneritore industriale, 1999-2014

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ABSTRACT

BACKGROUND: exposure to dioxins has been associated with an increased risk of soft-tissue sarcoma (STS). In a study relating to 1989-1998, a significant excess of STS was found in the population living within a 2-kilometre radius of an industrial incinerator located inside a Mantua industrial site. In the years 1974-1991, the incinerator burned hazardous chlorine-containing waste that resulted in the emission of dioxins. After 1991, it was exclusively fed with organic synthetic products not containing chlorine.

OBJECTIVES: the aim of this case-control study was to estimate the STS risk, for 1999-2014, in the population living in four Mantua districts located in the proximity of the industrial incinerator, compared to subjects resident in the remaining parts of Mantua province, regarded as non-exposed.

METHODS: the cases analysed were subjects with a first-incident diagnosis of STS between 1999 and 2014 resident at diagnosis in Mantua Province. Cases were selected using the 2013 criteria from the WHO classification. Cases of Kaposi sarcoma, PEComas and STS occurring in a previously irradiated field were excluded. For each case of soft-tissue sarcoma, four controls were randomly selected from all individuals resident in Mantua Province included in the Regional Health Service database in the years of incidence of each case (calendar year), and individually matched for gender and year of birth. Residential and occupational history (for employment in an oil refinery, and petrochemical and chemical plants) was reconstructed for all study subjects (cases and controls) since 1961. Subjects were considered exposed if they had lived in the four Mantua districts most affected by the incinerator emissions, on the basis of an atmospheric dispersion model and a dioxins biomonitoring survey. Four analyses were performed according to variously defined residential time windows. Odds ratios and corresponding 95% confidence intervals (95%CI) were calculated using conditional regression models adjusted for occupational history.

RESULTS: 391 cases (203 males and 188 females) and 1,564 controls were included. The number of exposed cases and controls in the four analyses were 8 and 55, 8 and 60, 15 and 68, and 15 and 73, respectively. An increased STS risk was not observed in any of the analyses.

CONCLUSIONS: in this study, no increased risk of STS was observed in subjects who had lived, in the study's time window, in the Mantua districts most affected by the incinerator emissions. The most likely interpretation of the present finding is a real STS risk reduction for subjects resident in the most recent decades in the Mantua districts most affected by the incinerator emissions, due to the cessation of burning chlorine-containing waste in the incinerator, development of some remediation plans, and implementation of new industrial procedures.

WHAT IS ALREADY KNOWN

- **Increased risk of soft-tissue sarcoma has been reported in populations living in the proximity of incinerators characterised by significant emission of dioxins.**
- **A significant excess of soft-tissue sarcomas, relating to 1989-1998, was found in the population living within a 2-kilometre radius of a hazardous waste incinerator, located inside the Mantua industrial site. At the end of 1991, the incinerator stopped burning hazardous chlorine-containing waste.**

WHAT THIS PAPER ADDS

- **Results show that the population living in the four Mantua districts most affected by the incinerator emissions did not have an increased risk of soft-tissue sarcoma in the study time window (1999-2014), after the cessation of uncontrolled incineration of hazardous chlorine-containing waste, the implementation of new industrial procedures in Mantua facilities, and development of some remediation plans.**
- **The results of the study should contribute to the adoption of remediation action aimed at reducing emissions of dioxins into the environment, and consequently preventing the occurrence of soft-tissue sarcoma in the population living in the proximity of hazardous waste incinerators or other dioxin-emitting sources.**

Keywords: soft-tissue sarcoma, hazardous waste, incineration, dioxins, case-control study

RIASSUNTO

INTRODUZIONE: l'esposizione a diossine è stata associata a un aumento del rischio di sarcomi dei tessuti molli (STM). In uno studio, riferito al periodo 1989-1998, era stato osservato un importante eccesso di STM nella popolazione residente nel raggio di 2 chilometri di un inceneritore industriale situato all'interno del polo industriale di Mantova. Dal 1974 al 1991, l'inceneritore aveva bruciato rifiuti tossici, anche clorurati, con un conseguente rilascio di diossine in ambiente; dopo il 1991 è stato alimentato esclusivamente con prodotti organici di sintesi non contenenti cloro.

OBIETTIVI: scopo del presente studio caso-controllo è stato di stimare il rischio di STM, nel periodo1999-2014, nella popolazione che aveva vissuto in quattro quartieri di Mantova situati in prossimità dell'inceneritore industriale, rispetto alla popolazione residente nel resto della provincia di Mantova considerata non esposta.
METODI: sono stati considerati casi i soggetti con prima diagnosi di STM negli anni 1999-2014 e residenti al momento della diagnosi nella provincia di Mantova. I casi sono stati selezionati secondo i criteri riportati nella classificazione 2013 dell'OMS. Sono stati esclusi i casi con diagnosi di sarcoma di Kaposi e PEComa e i casi di STM insorti in un'area del corpo precedentemente trattata con radioterapia. Per ogni caso sono stati estratti casualmente quattro controlli dall'anagrafe assistiti di Mantova, appaiati per genere e anno nascita. È stata ricostruita la storia residenziale e occupazionale (per impiego in raffineria e impianti petrolchimici e chimici) di tutti i soggetti in studio (casi e controlli) dal 1961. Sono stati definiti esposti i soggetti che avevano risieduto nei quattro quartieri di Mantova maggiormente interessati dalle emissioni dell'inceneritore, sulla base di un modello di dispersione e di uno studio di biomonitoraggio delle diossine. Sono state effettuate quattro analisi in base a specifiche finestre temporali di residenza nell'area esposta. Le odds ratios e i relativi intervalli di confidenza al 95% sono stati calcolati applicando un modello di regressione condizionata aggiustato per occupazione.
RISULTATI: lo studio ha incluso 391 casi (203 maschi e 188 femmine) e 1.564 controlli. Il numero dei casi e controlli esposti nelle quattro analisi è risultato essere, rispettivamente: 8 e 55, 8 e 60, 15 e 68, 15 e 73. In nessuna delle analisi è stato osservato un aumento del rischio di STM nella popolazione esposta.
CONCLUSIONI: nel presente studio non è stato osservato un aumento del rischio di STS nelle persone che, nel periodo in studio, avevano vissuto nei quartieri di Mantova maggiormente esposti alle emissioni dell'inceneritore. L'interpretazione più probabile degli attuali risultati è di una effettiva riduzione del rischio per le persone residenti negli ultimi decenni nei quartieri maggiormente esposti alle emissioni dell'inceneritore a seguito del cessato incenerimento incontrollato di rifiuti contenenti cloro, alla messa in atto di opere di bonifica e all'aggiornamento tecnologico degli impianti.

Parole chiave: sarcoma dei tessuti molli, rifiuti pericolosi, incenerimento, diossine, studio caso-controllo

INTRODUCTION

Soft-tissue sarcomas (STS) are a complex group of rare malignant tumours with over 70 subtypes, which are very heterogeneous for primary site, histological subtype, gender predilection, and age at diagnosis.[1,2] Little is known about the aetiology of STS.[3] Increased risk of STS has been reported for occupational or environmental exposures to some dioxins (generic term for polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzo-*p*-furans, PCDD/PCDF), particularly to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), to chlorophenols or chlorophenoxy acid herbicides contaminated with dioxins, and to vinyl chloride (for angiosarcoma of the liver).[2,4-9] Other factors that have been associated with STS include some inherited genetic conditions and prior exposure to radiation therapy.[2,10]

Dioxins belong to the category of persistent organic pollutants. They are not produced intentionally but are by-products of combustion, incineration and various industrial processes. High levels of dioxins may be emitted from municipal, hospital and hazardous chlorine-containing waste incineration. Moreover, emissions of dioxins have been reported from metallurgical and petrochemical industries, oil refineries, electric power plants and paper mills. They are also formed during the production of some halogenated organic chemicals.[11-13]

The most recent evaluation by the International Agency for Research on Cancer (IARC) currently classifies TCDD, the most toxic member of its class, and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) as carcinogenic to humans (Group 1, established human carcinogen).[14]

According to the IARC, TCDD is carcinogenic to humans (Sufficient Evidence) for all cancer sites combined and the association between TCDD and soft-tissue sarcomas has been evaluated as based on Limited Evidence in humans.[15] Few population studies have been conducted to determine the relationship between STS and residence near incinerators characterised by significant dioxin emissions. Viel et al. (2000) examined the spatial distribution of STS around a French municipal solid waste incinerator (MSWI) with high emission levels of TCDD. They found a significant cluster (p 0.004) of STS around the MSWI, which was made up of two cantons: Besançon (where the plant was located) and Audeux (contiguous to the former). The standardised incidence ratio, based on 45 cases, was 1.44.[16] In relation to the Viel et al. (2000) study previously cited, Floret et al. (2004) designed a microspatial study on Besançon city to test the association between exposure to dioxins emitted by the municipal solid waste incinerator and risk of STS. Ground-level concentrations of TCDD were investigated using a dispersion model. Four increasing zones of exposure were defined. The Authors found that, compared with the least exposed zone, the risk of developing STS was not significantly increased for people living in the more exposed zones.[17] Fabre et al. (2007) conducted a retrospective ecological study on the cancer incidence around sixteen MSWIs in France. They observed a positive association between exposure to TCDD and STS incidence.[18] Zambon et al. (2007) conducted a case-control study to evaluate STS risk in relation to environmental pollution caused by TCDD emitted by waste incinerators and industrial sources of airborne emissions in a part of the Province of Venice (Italy). They found a risk of devel-

oping STS 3.3 times higher, which increased with both duration of exposure and modelled intensity of exposure to incinerator emissions.[19]

Comba et al. (2003) conducted a case control-study to estimate the incidence of STS diagnosed between 1989 and 1998 in the population living in the proximity of the industrial incinerator located inside the Mantua industrial site (Lombardy Region, Northern Italy). In the years from 1974 to 1991, the incinerator burned several types of hazardous chlorine-containing waste that resulted in the release of dioxins into the environment. Comba et al. found an excess incidence of STS (OR 31.4; 95%CI 5.6-176.1) associated with residence within a 2-kilometre radius of the incinerator.[20]

A systematic review of epidemiological studies published between 1983 and 2008 defined the evidence of the association between STS and living within 3 kilometres of an old incinerator as "limited", with a Relative Risk equal to 1.16 (95%CI 0.96-1.41).[21]

A more recent WHO Report on the health effects of waste management reports that the studies performed on the risk of STS in the population living near old incinerators (active in the years 1969-1996) indicate interesting but not consistent results.[22]

The aim of this case-control study was to investigate the STS risk for 1999-2014 in the population living in four Mantua districts located in the proximity of the industrial incinerator, compared to subjects resident in the remaining parts of Mantua province, regarded as non-exposed. In this study, the methodological approach was partially different from that used by Comba et al. (2003)[20] in their study, relating to 1989-1998, on STS risk in the population living in the proximity of the Mantua industrial incinerator.

METHODS

AREA DESCRIPTION

Mantua is a town of about 50,000 inhabitants. An industrial settlement was created in the neighbourhood along the Mincio River in the decade 1950-1960. The industrial area grew in the direction of the urban area. Three districts – Virgiliana, Frassino, and Lunetta – have part of their territories within 2 kilometres of the stacks in the industrial site. The industrial site is, or was in the past, characterised by the presence of several polluting sources: a major oil refinery, a petrochemical plant, three thermoelectric power plants, some large combustion plants, a chemical plant, a metallurgical facility, a dockyard, three hazardous waste landfills, and an incinerator for industrial and sanitary waste. Moreover, in an area located in the proximity of the industrial site, a major paper mill has been operating since 1902. Since the 1980s, that mill has produced recycled paper, using chlorine as a bleaching agent. All these activities produced emissions and releases

Figure 1. Study area.
Figura 1. Area in studio.

of pollutants into the environment in the air, groundwater, soil and the Mincio River.[23-25]

The oil refinery had a set of tanks containing about 196,000 m^3 of crude oil and 460,000 m^3 of products, and a torch operating full time was used as for incineration.[24] The oil refinery stopped operating in 2013. The petrochemical plant was a leader in styrene/polystyrene and phenol production. Cracking and chlorosoda production were terminated between 1986 and 1997.[25]

With regard to the pollutants of interest for this study (dioxins), because of the large amount of hazardous chlorine-containing waste burned, the industrial incinerator might reasonably be considered as the major contributor to emissions, even if some of the other activities mentioned above might also have contributed to the release of dioxins into the environment.

The industrial and sanitary waste incinerator treated about 12,000 tons of waste per year.[23] It was able to treat 1,000 kg/h of liquid and 750 kg/h of solid waste each day, with temperatures reaching up to 950°C. During 1974-1991, it incinerated process water, exhaust solvents, tar, pitch, exhaust resins, industrial muds, plastic, papers, glues, varnishes, drugs, veterinary products, cosmetics, hospital waste, and miscellaneous waste produced by the agriculture and food industry. Most of this waste was classified as toxic.

The incinerator stack was 30 m high with a diameter of 1.20 m, and the emission rate was about 30,000 m^3 per hour.[25] Even in the absence of published reports on the stack emissions, the existence of the following contaminants has been reported: particulate matters, SO_2, CO,

CO_2, heavy metals, polychlorinated biphenyls (PCBs), polycyclic-aromatic hydrocarbons (PAHs), dioxins, total organic compounds and other chemicals.[26]

At the end of 1991, the incinerator stopped burning hazardous chlorine-containing waste, and after 1991 it was fed exclusively with organic synthetic products not containing chlorine.

An atmospheric dispersion model based on SO_2 as a tracer of industrial emissions suggested that the districts of Mantua most affected were Frassino, Virgiliana, Lunetta (north-west of the industrial incinerator) and Valletta-Valsecchi (towards the city centre) (figure1).[26] The air dispersion model was developed taking into account all the emission sources located in the industrial area.

In a biomonitoring survey conducted among Mantua residents, a statistically significant higher level of some dioxins was found in subjects resident near the industrial area compared to those living in the city centre (see in detail below).[27] In light of the aforementioned results of the atmospheric dispersion model and biomonitoring survey, this investigation defined the Mantua districts of Virgiliana, Frassino, Lunetta and Valletta-Valsecchi as the exposed area.

CASES AND CONTROLS DEFINITION

The cases analysed were subjects, of all age, with a first-incident histologically confirmed diagnosis of malignant soft-tissue sarcoma originating at any anatomical site (limbs, somatic soft-tissue of the trunk, head and neck, retroperitoneum, peritoneum, mediastinum, skin and visceral organs), except bones and joints, diagnosed for the first time in the period 1999-2014, and resident at the time of diagnosis in Mantua Province.

Inclusion was based on the criteria specified on the fourth edition of the World Health Organisation Classification of Tumours of Soft-tissue and Bone published in 2013 (hereafter the "2013 WHO classification" for simplicity)[28] and the recommendations of an expert STS pathologist.

The 2013 WHO classification contains major modifications compared to the previous version through the addition of new chapters (gastrointestinal stromal tumours, nerve sheath tumours, undifferentiated/unclassified sarcomas), inclusion of new entities (e.g., epithelioid malignant peripheral nerve sheath tumour, PEComas), deletion and reclassification of some entities (e.g., pleomorphic malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma now included in the category Tumours of Uncertain Differentiation), and renaming of some tumours (e.g., round cell liposarcoma now known as myxoid liposarcoma).[29]

Because of the reclassification and renaming of several entities in the 2013 WHO classification, and considering that the majority of the subjects included in this study were diagnosed before or one year after the 2013 WHO publication, we also included some histotypes according to the morphological codes used in previous classifications.

All the histological types were linked to the corresponding morphological codes from the International Classification of Diseases for Oncology, third edition (ICD-O-3).[30] We did not include:

1 Kaposi sarcoma, which is essentially related to human herpesvirus 8 (HHV-8) and human immunodeficiency virus (HIV) infection;[2]

2 STS occurring in an area of body previously treated with radiotherapy within 20 years before the STS diagnosis and with a minimum latency period of three years, as the role of therapeutic radiation in inducing STS is well established;[2,31]

3 PEComas, as this term was only codified in the ICD-O-3 only in 2012 and there are no clearly defined criteria of malignancy.[32]

For individuals with more than one STS diagnosis, only the first diagnosis was assessed to determine if the case met eligibility criteria.

The ICD-O-3 morphological codes included were: 8711, <u>8800-8806</u>, 8810, 8811, 8814, 8815, 8825, <u>8830</u>, 8832, 8833,8840, 8842, 8850, <u>8851</u>, 8852, <u>8853</u>, 8854, <u>8855</u>, <u>8857</u>, 8858, 8890, <u>8891</u>, 8895, <u>8896</u>, <u>8900</u>, 8901, <u>8902</u>, 8910, 8912, 8920, 8921, 8936, 8940, 8963,8963, 8964, 8990, 8991, 9040, 9041, <u>9042</u>, 9043, 9044, 9120, 9130, 9133, <u>9150</u>, 9170, 9180, <u>9181</u>, 9220, 9231, 9240, <u>9251</u>, 9252, <u>9260</u>, 9364, <u>9365</u>, <u>9473</u>, <u>9540</u>, 9542, <u>9560</u>, 9561, 9571, 9580, 9581; Behaviour/3 (the underlined codes refer to classifications prior to the 2013 WHO classification). The ICD-O-3 topographical codes of STS site of origin were: C38.1, C38.2, V38.3, C47, C48, C49, C76, and organ-specific codes.

Incident cases were obtained from the Mantua Cancer Registry, which has coverage of 100% of the territory of Mantua Province. Information collected by the register includes general demographic characteristics of the patients (age, gender, and municipality of residence), site and histological type of the tumour, and time of diagnosis. The case-ascertainment procedure did not include a pathological review of the specimens, but detailed scrutiny of the pathological reports and clinical records was performed.

For each case of soft-tissue sarcoma, four controls were randomly selected from all individuals resident in Mantua Province included in the Regional Health Service database and individually matched for gender, year of birth and calendar year.

RESIDENTIAL AND OCCUPATIONAL HISTORY

Residential history was reconstructed for all subjects included in the study (cases and controls) from 1 January 1961 to the date of diagnosis for cases and to the date

of enrolment for controls. Data on residential history were gathered from the Mantua Municipal Registrar's Office. Moreover, in order to identify subjects with an occupational history in the petrochemical plants, chemical plants and oil refinery, two record linkages were performed, both for cases and controls: one with the National Institute of Social Security (INPS) database and another with the occupational cohorts of the industries located in the Mantua industrial site. The linkage with the Social Security files, supplemented by a linkage with the database of the cohort study performed by the Mantua Health Authorities, has provided information on the work activity of 59% of the cohort members with respect to occupation in the oil refinery and chemical plants. No significant difference in terms of frequency of activity in these industries has been observed between cases and controls.

DESIGN OF ANALYSIS

We conducted a population-based case-control study. Four separate statistical analyses using conditional regression models adjusted for occupational history (oil refinery, petrochemical and chemical plants) were performed using Stata 14 to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (95%CIs). For each statistical analysis, a different residential exposure was defined, according to pre-established residential time windows in the exposed area (Mantua districts of Virgiliana, Frassino, Lunetta and Valletta-Valsecchi), and after excluding ten years preceding diagnosis for cases or at recruitment (defined as the reference diagnosis year for the corresponding case) for controls. The period of ten years before the diagnosis was excluded in order to account for a minimum latency period,[18] and this was applied only to subjects aged 20 years and over.

ANALYSIS 1. The odds ratio was estimated considering exposure in the years 1961-1991 (highest exposure period), in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls. This residential exposure was defined as "Residential Exposure 1".

ANALYSIS 2. The odds ratio was estimated considering exposure from 1961 onwards, in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls. This residential exposure was defined as "Residential Exposure 2".

ANALYSIS 3. The odds ratio was estimated considering exposure in the years 1961-1991 (highest exposure period). This residential exposure was defined as "Residential Exposure 3".

ANALYSIS 4. The odds ratio was estimated considering exposure from 1961 onwards. This residential exposure was defined as "Residential Exposure 4" (table 1).

In each analysis, subjects (cases and controls) that had resided in the exposed area in a period different from the time window considered in the definition of exposure were regarded as non-exposed (as shown in table 2 and 3). The rationale for performing four different types of statistical analyses was based on the following reasons:

- little is known about the latency time between exposure to dioxins and the occurrence of STS. The few data available, mainly concerning occupational exposure, report a latency time ranging from 12 to 30 years,[33-35] and no data are available on environmental exposure: we therefore decided to develop two different types of analyses, one taking into account residence in the time-window between 30 and 10 years before the diagnosis (Analysis 1, Analysis 2) , and another without this restriction (Analysis 3, Analysis 4);
- the period in which there was the highest exposure to dioxins was up to 1991. However, even after the year 1991, for some periods and because of former industrial activities, dioxins were probably still present in several environmental matrices (soil, water).[36] We therefore decided to develop two other types of analyses, one taking into account residence in the exposed area only in the years 1961-1991 (Analysis 1, Analysis 3), another also considering residence in 1961 and beyond (Analysis 2, Analysis 4).

RESULTS

There were 400 cases with a diagnosis of STS taken from the Mantua Cancer Registry and residing at diagnosis in Mantua Province. Nine cases were excluded as the STS occurred in the same part of the body previously treated with radiotherapy for another type of cancer. Therefore, 391 cases were finally included in the study - 203 males (aged 1-94, median age at diagnosis 61.1) and 188 females (aged 0-95, median age at diagnosis 59.4).

Among soft-tissue sarcoma cases and controls meeting the inclusion criteria, ORs were calculated for 8-15 cases and 55-73 controls, defined as exposed, depending on the definition of residential exposure.

The median years of residence in the exposed areas for exposed cases and controls are shown in table 2. In the exposed area, the median residence periods for controls are similar (Residential Exposure 1 and 2) or higher (Residential Exposure 3 and 4) than those for cases groups.

Table 3 shows ORs and their corresponding 95% confidence intervals for the four analyses performed according to variously defined residential exposures (Residential Exposure 1, Residential Exposure 2, Residential Exposure 3, Residential Exposure 4, see Methods), and adjusted for occupational history. No risk of soft-tissue sarcomas associated with residential exposure was found in any of the four analyses.

ANALYSES	RESIDENTIAL EXPOSURE			EXCLUSION OF 10 YEARS° BEFORE DIAGNOSIS* OR RECRUITMENT§
	BETWEEN 1961 AND 1991#	FROM 1961 ONWORDS	BETWEEN 30 AND 10 BEFORE DIAGNOSIS	
Analysis 1	✖		✖	✖
Analysis 2		✖	✖	✖
Analysis 3	✖			✖
Analysis 4		✖		✖

Highest exposure period / *Periodo di massima esposizione* ° Only for subjects aged 20 years or more / *Solo per i soggetti di età uguale o superiore a 20 anni*
* For cases / *Per i casi* § For controls / *Per i controlli*

Table 1. Synthetic description of the statistical analyses performed according to the four different definition of residential exposure.
Tabella 1. Descrizione sintetica delle analisi statistiche eseguite per le diverse esposizioni residenziali considerate.

	MEDIAN RESIDENCE RESIDENTIAL EXPOSURE 1^		MEDIAN RESIDENCE RESIDENTIAL EXPOSURE 2*		MEDIAN RESIDENCE RESIDENTIAL EXPOSURE 3†		MEDIAN RESIDENCE RESIDENTIAL EXPOSURE 4°	
	NUMBER OF SUBJECTS	NUMBER OF YEARS	NUMBER OF SUBJECTS	NUMBER OF YEARS	NUMBER OF SUBJECTS	NUMBER OF YEARS	NUMBER OF SUBJECTS	NUMBER OF YEARS
Cases	8	5.34	8	5.34	15	3.21	15	3.21
Controls	55	5.20	60	7.80	68	8.40	73	13.00

^ Exposure in the years 1961-1991 (highest exposure period), in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls.
Esposizione negli anni 1961-1991 (periodo di massima esposizione), nella finestra temporale compresa tra 30 e 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
* Exposure from 1961 and over, in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls.
Esposizione dal 1961 in poi, nella finestra temporale compresa tra 30 e 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
† Exposure in the years 1961-1991 (highest exposure period), after removing 10 years before diagnosis.
Esposizione negli anni 1961-1991 (periodo di massima esposizione), escludendo 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
° Exposure from 1961 and over, 10 years before diagnosis for cases and before recruitment for controls.
Esposizione dal 1961 in poi, escludendo 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.

Table 2. Median years of residence in the exposed areas for exposed cases and controls, according to Residential Exposure 1, Residential Exposure 2, Residential Exposure 3, and Residential Exposure 4.
Tabella 2. La mediana degli anni di residenza nell'area esposta dei casi e dei controlli nell'Esposizione residenziale 1, l'Esposizione residenziale 2, l'Esposizione residenziale 3 e nell'Esposizione residenziale 4.

TYPE OF EXPOSURE†	EXPOSED CASES	EXPOSED CONTROLS	OR	95%CI
Residential Exposure 1^	8	55	0.57	0.27-1.21
Residential Exposure 2*	8	60	0.52	0.24-1.10
Residential Exposure 3†	15	68	0.88	0.50-1.55
Residential Exposure 4°	15	73	0.81	0.46-1.43

^ Exposure in the years 1961-1991 (highest exposure period), in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls.
Esposizione negli anni 1961-1991 (periodo di massima esposizione), nella finestra temporale compresa tra 30 e 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
* Exposure from 1961 and over, in the time-window between 30 and 10 years prior to diagnosis for cases and before recruitment for controls.
Esposizione dal 1961 in poi, nella finestra temporale compresa tra 30 e 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
† Exposure in the years 1961-1991 (highest exposure period), excluding 10 years before diagnosis for cases and before recruitment for controls.
Esposizione negli anni 1961-1991 (periodo di massima esposizione), escludendo 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.
° Exposure from 1961 and over, excluding 10 years before diagnosis for cases and before recruitment for controls.
Esposizione dal 1961 in poi, escludendo 10 anni prima della diagnosi per i casi e dell'arruolamento per i controlli.

Table 3. Odds ratios (ORs) and 95% Confidence Interval (95%CI) for Soft-Tissue Sarcoma according to four differently defined residential exposures (from January 1st, 1961), and adjusted for occupational history (for employment in oil refinery, and petrochemical and chemical plants.), 1999-2014.
Tabella 3. Odds ratio (OR) e intervalli di confidenza al 95% (95%CI) dei sarcoma dei tessuti molli, per le diverse definizioni di esposizione residenziale (dal primo gennaio 1961), aggiustate per storia occupazionale (per l'impiego in raffineria e in impianti petrolchimici e chimici), 1999-2014.

DISCUSSION

The results of the analyses did not show an excess STS risk for the subjects that had lived within the study's time window in the four Mantua districts most affected by the industrial incinerator emissions.

Before a critical evaluation of the study findings, we should make some comments on validity issues and differences in the methodologies adopted in this study and in Comba et al. (2003).[20] The first question to be addressed is case definition. Because of changes in the classification of STS over the past two decades, some differences in the inclusion of morphological types between the Comba et al. and this study might exist. However, it is worth nothing that Comba et al., and this study, also included 1) the morphological types corresponding to the category "Nerve sheath tumours" in the 2013 WHO classification, as well as some morphological types corresponding to the category "Undifferentiated/unclassified sarcoma", and 2) some histotypes previously misclassified as other types of STS[37] and currently classified as "Gastrointestinal stromal tumours" in the 2013 WHO classification. Thus, the morphological types included in Comba et al. are quite similar to those include in this study. However, one difference between the two studies is that in this study, cases occurring in the area of the body previously treated with radiotherapy were excluded, whereas in Comba et al. these cases were not excluded.

The second aspect of the study design that needs to be discussed is the assessment of exposure. In the absence of an exposure categorisation based on dioxin environmental monitoring, it seemed reasonable to use data derived from an atmospheric dispersion model based on SO_2 as a tracer of industrial emissions, and a dioxins biomonitoring survey as an indirect exposure estimate.

These data showed that, according to the dispersion model,[26] the districts defined as the exposed area in this study were the most affected by industrial emission, and, according to the dioxins biomonitoring, were the most affected by dioxin emissions.[27] These districts fall almost entirely within a 2-kilometre radius of the incinerator, a radius within which Comba et al. observed an excess incidence of STS.

One limitation of this study is the small sample size, but it is worth noting that STS are very rare neoplasms (they represent about 1% of all malignancies in adulthood and 12% in the paediatric cancer population). Due to the small sample size, a specific comment on the study's statistical power is required. When dealing with the association between rare diseases and localized sources of exposure, not much can be done besides enlarging the time window of case selection and the matching ratio (the latter, in the frame of case-control studies). Both these procedures have been adopted in this study, obviously considering the inherent limits of the study time window in order to be consistent with its aims, and the lack of benefits of further increases in the control: case ratio after having reached an empirically reasonable threshold. Finally, what appears more relevant, is to look a posteriori at the precision of estimates of the odds ratios, that appears to be acceptable and consistent in the four sets of analyses. The absence of specific monitoring data exclusively regarding industrial incinerator dioxin emissions might be considered as another limitation. However, as noted above, the incinerator might reasonably be considered as the major contributor to dioxin emissions even if other activities might have contributed to the release of dioxins into the environment.

The potential confounding role of occupational exposures in agriculture has not been considered, since the Mantua area is mainly characterised by swine breeding and corn crops, for which the historical use of dioxin-containing herbicides/pesticides is unlikely. No factories processing fungicide-impregnated lumber are present in the study area.

The strength of this study is that the lack of association between residence in the four Mantua districts most affected by incinerator emissions and occurrence of STS in the study's time window seems well assessed, in light of its consistency under four different models. Furthermore, due to the availability of Cancer Registry data, the case series is complete and, with respect to the validity, complies with the requisites of the International Agency for Research on Cancer. Moreover, due to the methodological approach, the study is not affected by recall bias, since no information has been acquired by interviews with patients or their next-of-kin. Obviously, the latter point might also be seen as a weakness as it was not possible to collect individual data on potential confounders, with the exception of some specific occupational activity as mentioned above.

Although some methodological differences exist between this study and that of Comba et al. (2003),[20] they alone cannot explain the disappearance of the STS risk observed in the present study. The most likely interpretation of the current negative findings is a real risk reduction, following the cessation of uncontrolled incineration of hazardous chlorine-containing waste, for subjects resident in the most recent decades in the Mantua districts most affected by the incinerator emissions. Only three cases lived in the most exposed area of Frassino and Virgiliana. None of the STS cases had lived exclusively in the area after 1991, the year when the uncontrolled incineration of hazardous waste ceased. This is in agreement with the results of a biomonitoring survey of residents in Mantua (30 subjects living near the industrial area and 30 living in the town centre) conducted in 2005 to measure plasma levels of 27 dioxin-like compounds (seven PCDD, ten PCDF and ten dioxin-like polychlorinated biphenyls – PCBs). A higher statistically

significant level of TEQ (toxicity equivalency) of PCDF and total-TEQ, expressed as a proportional ratio between mean and median, was found in subjects resident near the industrial area compared to those living in the city centre. However, an estimate of the total-TEQ plasma values relating to 15 years prior to the biological monitoring date showed an exposure not exceeding 84.5 ppt (parts per trillion), which is not consistent enough with the high risk of STM previously detected, even though the monitoring shows an exposure gradient with the distance from the polluting source. With reference to these data, the Authors concluded that the results might be representative of a decreasing phenomenon of emission that had its peak some decades ago.[27]

In conclusion, the observation of a localised excess risk of STS in the years 1989-98[20] has not been replicated in the present study (relating to 1999-2014). This might be consistent with the general trend reduction of exposure that was previously discussed, due to the cessation of uncontrolled incineration of hazardous waste, the implementation of new industrial procedures in Mantua facilities and development of some remediation plans. Moreover, the previously found excess could be related to massive acute exposure to dioxins occurring before 1991.[38] While an appropriate reconstruction of this event seems quite problematic, continuing epidemiological surveillance of STS in Mantua appears to be warranted.

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Ethics approval, informed consent, and authorization from the Privacy Board: ethics approval and informed consent were not required. The study was based on current health information systems, and data analysis was based on anonymous aggregated data in the absence of any contact with study subjects. No harm or even nuisance was inflicted to the study population, so that neither informed consent nor Ethical Committee revision nor approval was required. A waiver of authorization from the Privacy Board was not required as the record linkage with the administrative archives by fiscal code is an institutional task of the Lombardy Epidemiological Observatory; it have to guarantee privacy but with respect to all other data users. The Lombardy Epidemiological Observatory provided the data in an anonymous form to the researchers involved in the study.

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