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Cancer incidence in Italian contaminated sites

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Abstract
Introduction. The incidence of cancer among residents in sites contaminated by pollutants with a possible health impact is not adequately studied. In Italy, SENTIERI Project (Epidemiological study of residents in National Priority Contaminated Sites, NPCSs) was implemented to study major health outcomes for residents in 44 NPCSs.
Methods. The Italian Association of Cancer Registries (AIRTUM) records cancer incidence in 23 NPCSs. For each NPCSs, the incidence of all malignant cancers combined and 35 cancer sites (coded according to ICD-10), was analysed (1996-2005). The observed cases were compared to the expected based on age (5-year period,18 classes), gender, calendar period (1996-2000; 2001-2005), geographical area (North-Centre and Centre-South) and cancer sites specific rates. Standardized Incidence Ratios (SIR) with 90% Confidence Intervals were computed.
Results. In both genders an excess was observed for overall cancer incidence (9% in men and 7% in women) as well as for specific cancer sites (colon and rectum, liver, gallbladder, pancreas, lung, skin melanoma, bladder and Non Hodgkin lymphoma). Deficits were observed for gastric cancer in both genders, chronic lymphoid leukemia (men), malignant thyroid neoplasms, corpus uteri and connective and soft-tissue tumours and sarcomas (women).
Discussion. This report is, to our knowledge, the first one on cancer risk of residents in NPCSs. The study, although not aiming to estimate the cancer burden attributable to the environment as compared to occupation or life-style, supports the credibility of an etiologic role of environmental exposures in contaminated sites. Ongoing analyses focus on the interpretation of risk factors for excesses of specific cancer types overall and in specific NPCSs in relation to the presence of carcinogenic pollutants.

Key words
- contaminated sites
- environmental pollution
- cancer incidence

INTRODUCTION

According to WHO contaminated sites are "areas hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or groundwater, air, food-chain, resulting or being able to result in human health impacts" [1]. About 127 000 sites have been identified as contaminated in 33 European countries [2], a legacy of early industrialization and poor management practices.

Characterizing the health impact of contaminated sites involves a multidisciplinary approach, with a relevant role of epidemiology both in the analysis and evolving pattern of the health profiles of populations, and in the study of the associations between environmental exposures and health effects, according to specific hypotheses [1].

Protecting human health from exposure to environ-

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mental pollutants is a public health priority, but the burden of tumours among residents in areas contaminated by carcinogens is not adequately studied and the specific epidemiological literature on cancer risk in polluted areas is limited. In Italy, SENTIERI Project (Epidemiological study of residents in National Priority Contaminated Sites, NPCSs), funded by the Italian Ministry of Health, studied mortality among residents of 44 NPCSs included in the "National Environmental Remediation Programme" [3, 4].

The original feature of SENTIERI Project is the *a priori* evaluation of the epidemiological evidence on the causal association between 63 causes of death and residence in proximity of environmental sources of emission/release (chemical industries, petrochemicals and refineries, steel plants, power plants, mines and/or quarries, harbour areas, asbestos or other mineral fibres, landfills and incinerators). The evaluation, based on standardized methodology [3, 4] was carried out to minimize the risk for researchers to be data-driven when interpreting results. Results of mortality analyses were published for each NPCS and for all 44 NPCSs combined [5]. In the period 1995-2002 for a total of 403 692 deaths (men and women combined), an excess of 9969 deaths was observed, 4309 out of 9969 excess cases were from cancer deaths.

A recent development of SENTIERI Project is the study of cancer incidence in NPCSs served by cancer registries. As compared to mortality, cancer incidence allows to investigate shorter latency periods, is mainly based on pathologically confirmed data not influenced by differential survival rates possibly related to socio-economic deprivation, it accounts also for non lethal neoplasms. The Italian Association of Cancer Registries (AIRTUM, www.registri-tumori.it) records cancer incidence through population-based cancer registries. AIRTUM data are included in *Cancer incidence in five continents* published by the International Agency for Research on Cancer [6]. AIRTUM, funded by the Italian Ministry of Health, is involved in national [7] and international scientific collaborations [8].

The aim of the present study is to describe cancer incidence in populations living in NPCSs, as compared to populations not residing in these areas, thus integrating the previously reported cancer mortality data [4, 5]. Cancer incidence in all NPCSs combined is presented in this paper.

METHODS

Italian NPCSs mainly include industrial sites characterized by the presence of chemical, petrochemical and steel industries, toxic waste dump sites and sites contaminated by asbestos and fluoro-edenite fibres [9, 10].

AIRTUM cancer registries are active in 23 out of 44 NPCSs included in SENTIERI Project: 17 covering all age classes and six specialised in childhood cancer (0-19 years). The present investigation includes more than 2 000 000 people living in 23 NPCSs.

For each NPCSs, the incidence of all malignant cancers combined and 35 cancer sites, or groups of cancer sites, was computed. Cancer cases were coded according to the 10th International Classification of Diseases (ICD-10). *Figure 1* shows, for the 23 NPCSs, the geo-

Figure 1.
Italian National Priority Contaminated Sites: geographical distribution and main characteristics

NPCS	Registry population	NPCS population in AIRTUM database N.	NPCS population in AIRTUM database (%)	Period of Registry activity
1 *	4388	963	16	1996-2005
2 *	4488	1 114	17	1996-2005
3 *	57 874	13 399	15	1996-2005
4 *	5300	1 458	16	1996-2005
5 *	10 066	2 210	6	1996-2005
6	98 724	20 933	100	1996-2004
7	485 287	209 057	100	1999-2001, 2004-2005
8	189 168	59 905	100	1999-2004
9	453 346	104 029	100	1996-2005
10	498 488	116 298	100	1996-2005
11	149 704	32 040	100	1996-2005
12	1 005 201	205 535	100	1996-2005
13	1 316 195	270 884	100	1996-2005
14	202 337	46 247	100	1996-2005
15	505 706	117 863	100	1996-2005
16 *	22 784	4689	17	1996-2005
17 **	205 779	65 793	65	1996-2005
18	505 025	113 324	100	1996-2005
19	1 231 413	266 231	19	1996-2005
20	66 632	46 306	100	2003-2005
21	33 381	23 947	100	2003-2005
22	624 360	183 841	100	1999-2005
23	688 675	153 225	100	1996-2005
TOT.	**3 409 131**	**2 059 291**		

* childhood cancer registration
** adult and childhood cancer registration
NCPS: National Priority Contaminated Sites;
AIRTUM: Italian Association of Cancer Registries.

Table 1.
Cancer incidence in National Priority Contaminated Sites (NPCSs) in Italy, 1996-2005

ICD X – cancer site		Men				Women			
		Observed	SIR,	90% CI		Observed	SIR,	90% CI	
Total (skin C44 excluded)	Total, skin excluded	57391	1.09	1.08	1.1	49058	1.07	1.06	1.08
C15	Esophagus	697	1.22	1.14	1.29	230	1.24	1.11	1.38
C16	Stomach	2520	0.85	0.82	0.88	1932	0.84	0.81	0.88
C18-21	Colorectal	7204	1.05	1.03	1.07	6460	1.06	1.04	1.08
C22	Liver	3024	1.39	1.35	1.43	1419	1.32	1.26	1.37
C23-4	Gallbladder	589	1.12	1.04	1.19	951	1.12	1.06	1.18
C25	Pancreas	1543	1.12	1.08	1.17	1635	1.08	1.04	1.13
C32	Larynx	1575	1.19	1.14	1.24	193	1.43	1.27	1.61
C33-34	Lung	9396	1.07	1.05	1.09	3046	1.24	1.21	1.28
C40-41	Bone	104	0.97	0.82	1.14	94	1.04	0.87	1.23
C43	Skin melanoma	1280	1.24	1.18	1.29	1285	1.14	1.08	1.19
C45	Mesothelioma	469	1.88	1.74	2.03	110	1.11	0.94	1.3
C47,49	Connective and soft tissue	299	1.05	0.96	1.16	227	0.88	0.79	0.99
C47,49 (morphology codes)	Soft tissue sarcoma	272	1.07	0.97	1.19	195	0.86	0.76	0.97
C50	Breast	117	0.98	0.84	1.14	14387	1.08	1.07	1.1
C53	Cervix					848	1.03	0.98	1.09
C54	Corpus uteri					2119	0.96	0.92	0.99
C53-55	Uterus					3173	1.00	0.97	1.03
C56	Ovary					1603	1.01	0.97	1.06
C61	Prostate	10481	1.13	1.11	1.15				
C62	Testis	513	1.08	1.01	1.17				
C64-66,8	Kidney and other urinary organs	2156	1.08	1.05	1.12	1222	1.08	1.03	1.13
C67-D09.0,D30.3,D41.4	Bladder, total	5872	1.05	1.03	1.08	1601	1.15	1.11	1.2
C70-72	Brain and central nervous system	915	1.07	1.02	1.13	791	1.05	0.99	1.11
C73	Thyroid	457	0.98	0.91	1.07	1399	0.89	0.85	0.93
C81-96	Lymphoemopoietic tissue	4345	1.01	0.98	1.04	4098	1.04	1.01	1.07
C81	Hodgkin lymphoma	319	1.00	0.91	1.1	297	1.08	0.98	1.19
C82-85,96	Non-Hodgkin lymphoma	1926	1.06	1.02	1.1	1866	1.07	1.03	1.11
C88,90	Multiple myeloma	732	1.03	0.97	1.09	749	1.03	0.97	1.09
C91-95	Leukemia	1368	0.95	0.91	0.99	1186	1.00	0.95	1.05
C91.0-C91.1	Lymphoid leukemia	585	0.89	0.83	0.96	488	0.95	0.88	1.02
C91.0	Acute lymphoid leukemia	133	0.93	0.8	1.08	121	1.04	0.89	1.21
C91.1	Chronic lymphoid leukemia	452	0.88	0.82	0.95	367	0.93	0.85	1.01
C92.0-C92.1	Myeloid leukemia	544	1.02	0.95	1.09	495	1.05	0.97	1.13
C92.0	Acute myeloid leukemia	340	1.00	0.91	1.1	310	0.98	0.89	1.08
C92.1	Chronic myeloid leukemia	204	1.04	0.93	1.17	185	1.17	1.04	1.33
Total (skin C44 excluded)	Total, skin excluded	57391	1.09	1.08	1.1	49058	1.07	1.06	1.08
C15	Esophagus	697	1.22	1.14	1.29	230	1.24	1.11	1.38

[a] number of observed incident cases.
[b] SIR: Standardized Incidence Ratio, 90% CI: 90% Confidence Interval.

graphical distribution, population size and years of activity of each cancer registry. The observation period is 1996-2005. In 5 out of 23 areas the number of years of observation is less than 10 years, ranging from 3 to 7.

The number of observed cases for all malignancies and specific cancer sites was compared to the expected figures based on age in 5-years period (18 classes), gender, period (1996-2000; 2001-2005), area (North-Centre and Centre-South, not overlapping) and cancer sites specific rates. Two sets of geographical specific rates were calculated in light of a decreasing trend from north to south for the majority of cancer sites in Italy [11]. The populations from each NPCS and from two registries not participating to the study were excluded when calculating the expected. Standardized Incidence Ratios (SIRs) and 90% Confidence Intervals (90% CIs) were computed.

RESULTS

The overall study findings are reported in *Table 1*. In the overall analysis of 23 Italian contaminated sites served by cancer registries, on the basis of 57 391 and 49 058 incident cases respectively among men and women, an excess of cancer incidence (9% in men and 7% in women) was observed. The excess of all malignant neoplasms present in both genders was mainly explained by malignant neoplasms of colon and rectum (in men and women respectively 7204 cases, 5% increase and 6460 cases 6% increase), liver (in men and women respectively 3024 cases, 39% increase and 1419 cases 32% increase), gallbladder (in men and women respectively 589 cases, 12% increase and 951 cases 12% increase), pancreas (in men and women respectively 1543 cases, 12% increase and 1635 cases 8% increase), lung (in men and women respectively 9396 cases, 7% increase and 3046 cases 24% increase), skin melanoma (in men and women respectively 1280 cases, 24% increase and 1285 cases 14% increase), bladder (in men and women respectively 5872 cases, 5% increase and 1601 cases 15% increase) and Non Hodgkin lymphoma (in men and women respectively 1926 cases, 6% increase and 1886 cases 7% increase). Excesses of mesothelioma, and malignant neoplasms of prostate, testis, kidney and brain were present among men, among women increased incidence was present for breast cancer, lymphohaematopoietic system and in particular chronic myeloid leukemia. A deficit of gastric cancer was observed in both genders, deficits of total leukemias and specifically of (chronic) lymphoid leukemia were observed in men and, in women, deficits of malignant neoplasms of thyroid, *corpus uteri* and connective and soft-tissue tumours and sarcomas.

DISCUSSION

The assessment of the possible health impact of contaminated sites is a challenging issue, especially in the case of industrially contaminated sites involving multiple and heterogeneous human exposures. The methods used in the SENTIERI Project has been defined by WHO as a first level approach to describe population health profiles in contaminated areas [1].

The present report is, to our knowledge, the first one on cancer risk of communities resident in areas defined as National Priority Contaminated Sites. The excess of cancer incidence in the pooled analysis confirmed the previous observation of cancer mortality excess in 44 sites, 4.8% in men and 2.6% in women [4, 12].

Etiological hypotheses of a causal link between cancer incidence and residence in contaminated areas are present in the international scientific literature. There is general agreement, though, that an evaluation of sufficient evidence of causality cannot be formulated, the exception being pleural mesothelioma and residence near asbestos mines or asbestos industries, such as asbestos-cement plants. Recently, increasing evidence has been provided for associations between residence near: i) processing and storage facilities and lung cancer and Non Hodgkin lymphoma [13, 14]; ii) refineries, thermal power plants, steel and pulp mills and breast cancer [15]; iii) metal industries and prostate cancer [16] and digestive tract cancer [17]; iv) sites contaminated by toxic waste dumps and bladder and kidney cancer [18]. Increased incidence of haematological cancers, was observed in ZIP codes containing benzene waste sites [19]. A detailed review of this body of evidence has been recently published [20].

The present study did not aim to estimate the burden of tumours attributable to environmental exposures as compared to occupational exposures or life-style factors. However our results support the credibility of an etiologic role of *environmental exposures*, also in reason of several cancer excesses detected in both genders. Analytical studies, with improved exposure assessment, are needed to reach more firm conclusions.

The plausibility of the observed cancer excesses is supported by their consistency with the *a priori* hypothesized increases [3] and by the detailed report currently in press [21] on each of the 18 contaminated sites included in the present article.

In SENTIERI Project 90% CI were computed for risk estimators to present the range of uncertainty. Estimators were not accompanied by a hypothesis test to discriminate statistical significant from non statistical significant results. The choice of 90% level was made to minimize the acritical use of CI as surrogate of hypothesis testing; such use could lead to consider relevant only those estimators for which the CI exclude the null value, i.e. the ones customarily defined as "statistical significant" [22, 23]. The discriminating use of statistical significance in the evaluation of causal associations in epidemiology has been discussed since 1965 [24] and recently re-proposed [25]. This is particularly the case in SENTIERI Project where an *a priori* evaluation of the epidemiological evidence was completed to identify those diseases for which the causal association with the *environmental exposures* was either ascertained or probable. In SENTIERI the primary interest is on excesses or defects, i.e. direction of the risk estimators, and after on their size and precision, the latter inferred from the range of CI.

The strengths of the present study are the validity of cancer registration and the elevated number of cases included in the investigation, which ensures a high statistical power. The quality indicators of AIRTUM registries comply with the international standards [6]. In addition, specific checks are routinely performed using also a software developed by AIRTUM (Check-AIRTUM, www.registri-tumori.it). Furthermore, the selection of the study areas and the definition of *a priori* hypotheses has followed standardized and explicit criteria and procedures [3-5]. Major limitations of the investigation are the lack of a quantitative indicator of population exposure and the use of municipality as the smallest level of data aggregation.

Another limitation is that risk estimates are not adjusted for potential confounders such as alcohol consumption, smoking and socioeconomic status (SES), this last both positively and negatively associated with some cancers [3]. This lack of adjustment is most often the case in ecological studies. The overall estimates in the present paper were not adjusted for socioeconomic status (SES) although populations living in polluted areas have low SES [26]. This decision was based on a sensitivity analysis of *ad hoc* SENTIERI Deprivation Index which did not show substantial differences between unadjusted and adjusted risk estimates. As far as smoking and alcohol consumption are concerned, most cancer sites in excess have Sufficient or Limited evidence of association with tobacco or alcohol consumption [3]. There is no evidence that the *environmental exposures* in NPCSs are associated to either exposure, therefore the lack of adjustment should not lead to biased estimates.

Some underestimation of risk may derive from the incomplete coverage of cancer registration in some NPCSs. Developments of the multi-outcome SENTIERI approach include morbidity (as estimated by hospital discharge records), occurrence of congenital anomalies (pathology registries) and a specific focus on children health [27]. Ongoing analyses are focusing on the interpretation of cancer incidence in single NPCS, in relation to industrial emissions and/or releases from dumping sites as well as the presence of chemical carcinogens with evidence of association to specific tumours. Studies on the geographical distribution of cancer incidence based on individual data and environmental exposure modelling are also under way.

SENTIERI introduces a multiple outcome analytical model based on updated health outcomes in order to establish a permanent observation system to monitor the state of health of residents in contaminated areas. This will pave the way for more in-depth analytical epidemiological investigations and support the establishment and continued monitoring of primary prevention projects. In SENTIERI particular attention is devoted to issues of information and communication.

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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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