Ann Ist Super Sanità 2021 | Vol. 57, No. 2: 174-182
DOI: 10.4415/ANN_21_02_10

Original articles and reviews

Mortality temporal trends and cancer incidence profiles of residents in the petrochemical industrially contaminated town of Gela (Sicily, Italy)

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Abstract
Objective. In 2000, a vast area in Gela (Sicily, Italy) was defined as a national priority contaminated site due to pollution from a petrochemical complex. This study is aimed at addressing the influence of the petrochemical complex on the health profile of residents in Gela.
Methods. Trend analysis by gender was performed for mortality for all diseases and malignant cancers, in the period 1980-2014 for residents in the municipality of Gela, by directly standardized rates and Joinpoint regressions, using, as a reference population, people resident in the Sicily region. SMRs were computed for 5-year periods in the same timespan. Since the beginning of the period analyzed, the share of population of Gela represents 1.5% of total residents in Sicily. Cancer incidence was analyzed for the period 2007-2012 applying a hierarchical Bayesian model to estimate Standardized Incidence Ratios (SIR). Ranks of these ratios were computed to highlight the most incident diseases affecting the population. Malignant neoplasms of lung, stomach and colon were selected because of *a priori* interest, as they are associated, in etiological terms, with the main contaminants found in the area. Malignant neoplasms of liver, pancreas and larynx were selected as "control diseases" since they share the same main risk factors (smoke and alcohol consumption) of neoplasms of *a priori* interest, but are not associated with the priority index contaminants identified in Gela.
Results. Mortality rates for all causes combined in both genders in Gela decreased over time, but they were higher than those of the whole Sicilian population. The trend of mortality rates due to all malignant cancers increased in men, especially from 1980 to 1987. This result was confirmed by the Joinpoint regression (annual percentage change (APC) 9.8). SMRs analysis showed significant excesses in mortality due to all diseases for both genders compared to the reference population. Other excesses were observed for mortality due to malignant cancers in men and for circulatory diseases in women. The trend for cancers in women in Gela increased from the mid-nineties but less than in men. SIR estimates were higher than 1 for all the diseases analyzed and in both sexes, and their ranks highlighted that cancer sites of *a priori* interest hold higher positions than "control diseases", although credibility intervals overlapped.
Conclusions. Results highlight that the health profile of residents in Gela is worse than the one of the reference population. Moreover, cancer incidence is in excess in all the sites analyzed and mortality due to all cancers combined has a trend compatible with a cumulative impact due to petrochemical contamination.

Key words
- contaminated sites
- petrochemical industry
- mortality
- cancer incidence
- temporal trends

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INTRODUCTION

World Health Organization (WHO) defines contaminated sites as "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 able to result in human health impacts" [1]. In 1998 (law 426/98), in Gela (Sicily), a vast area close to the town was defined as national priority contaminated site due to pollution from a petrochemical complex built in 1960 and active since 1962. It hosted a large oil refinery, as well as thermoelectric power and petrochemical plants for production of organic and inorganic chemicals. The oil processing waste polluted the close environmental matrices: air, soil and, due to long time disposal, the stocked waste polluted also the groundwater. Moreover, a specific chemical waste, the Petcoke, was reused as a fuel for the thermoelectric power plant instead to be treated as dangerous waste.

In 2000, with the Legislative Decree, the area covering the entire petrochemical complex and an extended sea portion was officially identified to be remediated [2] and data gathered since the same year by the Istituto Superiore di Sanità (ISS, the Italian National Institute of Health) documented heavy groundwater, soil and air contamination [3].

After a first seizure in 2002, the industrial complex was gradually downsized until the closure in 2014. Then, a conversion of a small portion of the industrial site to renewable energy production was begun. Meanwhile, in 2009, environmental matrices analysis showed the presence of arsenic and heavy metals like lead and mercury (and vinyl chloride) thousand times more than the threshold values permitted by law [4]. In September 2019, a new bio refinery unit started its operations.

Focusing on the health profile of people in Gela, previous studies on residents and petrochemical site workers, showed excesses lung cancer mortality for both genders, hospitalizations due to acute and chronic respiratory diseases and pneumoconiosis, and congenital malformations of the nervous, cardiovascular and genitourinary systems [2; 5-7]. Exposure to some of the priority index contaminants identified in the polluted area is associated to several non-malignant diseases. Long-term arsenic assumption can cause diabetes and severe neurologic diseases [8], while exposure to lead is associated to neurotoxic effects and circulatory system diseases (i.e. hypertension) [9].

This study is aimed at evaluating the risk of mortality and cancer incidence for the population residing in Gela associable with the pollutants found in the widespread petrochemical contaminated area.

METHODS

Mortality and incidence are analyzed in this study. A trend analysis of mortality was made to focus on the evolution of the health profile of the population of residents in the municipality of Gela. The period considered is from 1980 to 2014, beginning twenty years after the start of activities of the petrochemical complex. Mortality for all diseases, malignant neoplasms (ICD10 codes C00-C97), four groups of causes relatives to the main systems (circulatory (I00-I99), respiratory (J00-J99), digestive (K00-K93) and genitourinary (N00-N99) and for malignant neoplasm of bronchus and lung (C34) was analysed using different tools. The latter disease was chosen because of the consistent results on excess of risk observed in other studies [2, 3]. Analyses were computed for both genders and for all ages.

Age directly standardized rates of death due to all diseases and to malignant neoplasms were computed for both genders, year by year, for the population residing in Gela and the entire Sicily. Standardized rates, computed having the Italian population of 2011 as reference, were calculated considering the first two twenty-year age classes (0-19, 20-39), and the others of ten-year, excluding the last one (80+). Simple centred moving averages (5-year periods) of rates for Gela's residents were used to improve their statistical stability. The Jointpoint regression [10] was applied to estimate the annual percentage changes (APCs). This estimator allows to highlight how rates change year by year and if the percentage change is statistically significant.

Standardized Mortality Ratios (SMRs) by gender were computed, with 90% confidence level, for the health profiles of residents in Gela (75,668 individuals)[1] considering the whole regional Sicilian population as reference (5,002,904 individuals)[1]. The Sicilian population was chosen as reference to balance the trade-off between similarity with the population of interest (in terms of lifestyles and habits) and the number of residents large enough to ensure stability of rates for age classes and rare diseases. SMRs were computed by gender for all diseases, malignant cancers, bronchus and lung cancer and for four groups of causes relatives to the main systems (respiratory, circulatory, digestive and genitourinary) splitting the whole period in five-year sub-periods. SMRs were computed for all ages, and for three macro-age classes (0-29, 30-64, 64+) and the specific age class 45-69. The last age class was chosen to maximize the difference, during the time window observed, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex. In 1980, first year with data available, people deceased in that age class were potentially exposed only for the last twenty years of life, while in 2014, last year with data available, people deceased were potentially exposed for almost the entire life.

Standardized Incidence Ratios (SIRs) were computed to analyze cancer incidence using data of the Caltanissetta province cancer registry to assess the cancer cases in the population of Gela in the 2007-2012 period. The population of regions belong to the macro area "South Italy and Islands" as reference (20,619,697 individuals)[1], using the methodological approach for cancer incidence data, applied in the last report of SENTIERI, the epidemiological surveillance system of residents in Italian main contaminated areas [3]. This approach was among those promoted within the Industrially Contaminated Sites and Health Net-

[1] People resident in Gela and Sicily in 2011, year of the last Census in Italy.

work (ICSHNet; www.icshnet.eu) to conduct descriptive studies for providing health profiles of populations living close to or in contaminated areas [11]. Twenty-two cancer sites for men and nineteen for women were considered. These sites were chosen considering the epidemiological evidences of association observed with the pollutants from the complex and are mutually exclusive. Some cancer sites were selected considering the health effects of the priority index contaminants identified following the methods developed in SENTIERI [3, pp. 180-188]. Following the evaluation of the epidemiological evidence of the association between specific causes and environmental exposures in SENTIERI [12], with regards to the typology of the complex, cancer sites of lung, stomach and colon were selected as *a priori* interest. Moreover, they are associable, in etiological terms, to some priority index contaminants found in the area (e.g. Arsenic, Cadmium, Chromium VI, Nickel, Lead). Malignant neoplasms of pancreas, larynx and liver (only pancreas and liver for women because cases of larynx neoplasm were not enough in the observation period (< 3)) were selected as control diseases since they have the same main risk factors associated to lifestyle (smoke and alcohol consumption) of cancer sites of *a priori* interest, but are not associable to the priority index contaminants identified in Gela [13]. SIRs were computed by means of a hierarchical Bayesian model based on Monte Carlo Markov Chain [14, 15]. In the applied Bayesian model, the data information (likelihood) was used choosing a non-informative prior distribution. The number of observed cases Y_i, has a Poisson distribution with parameter λ_i, as a product of the expected and known number of cases E_i, and the parameter of interest, the SIR, θ_i. The hierarchical structure of the model, defines that θ_i is defined by an *a priori* distribution with hyperparameters. In this case, the log transformation of θ_i has a Normal distribution with non-informative hyperparameters μ and $1/\sigma$ distributed, respectively, as a Normal (0, 0.0001) and a Gamma (0.1, 0.1). The rank of the estimated SIRs was calculated, with 80% credibility level, to highlight which diseases have the highest or lowest ratios [16]. Given K diseases, the rank of the disease *i* is defined by number of times the SIR of that disease is higher than the SIRs of other diseases.

RESULTS

Trend analysis of mortality for all diseases show that rates for men and women in Gela were decreasing over time, but they were always higher than the Sicilian ones (*Figure 1*). Gela's rates decreased from 205 deaths per 10,000 inhabitants to 135/10,000 in men and, from 185/10,000 to 100/10,000 in women. Sicilian rates decreased to 125/10,000 for men and 88/10,000 for women. The results from the trend analysis of mortality for all malignant cancers in Gela show an increase of rates from less than 25 deaths per 10,000 inhabitants (1980) to 45 deaths per 10,000 (2000) in men. From 2000 rates started to decrease to reach about 38/10,000 in 2014. There was an increase also for women but lower than in men, with the highest value, 25/10,000 (*Figure 2*), in 2004.

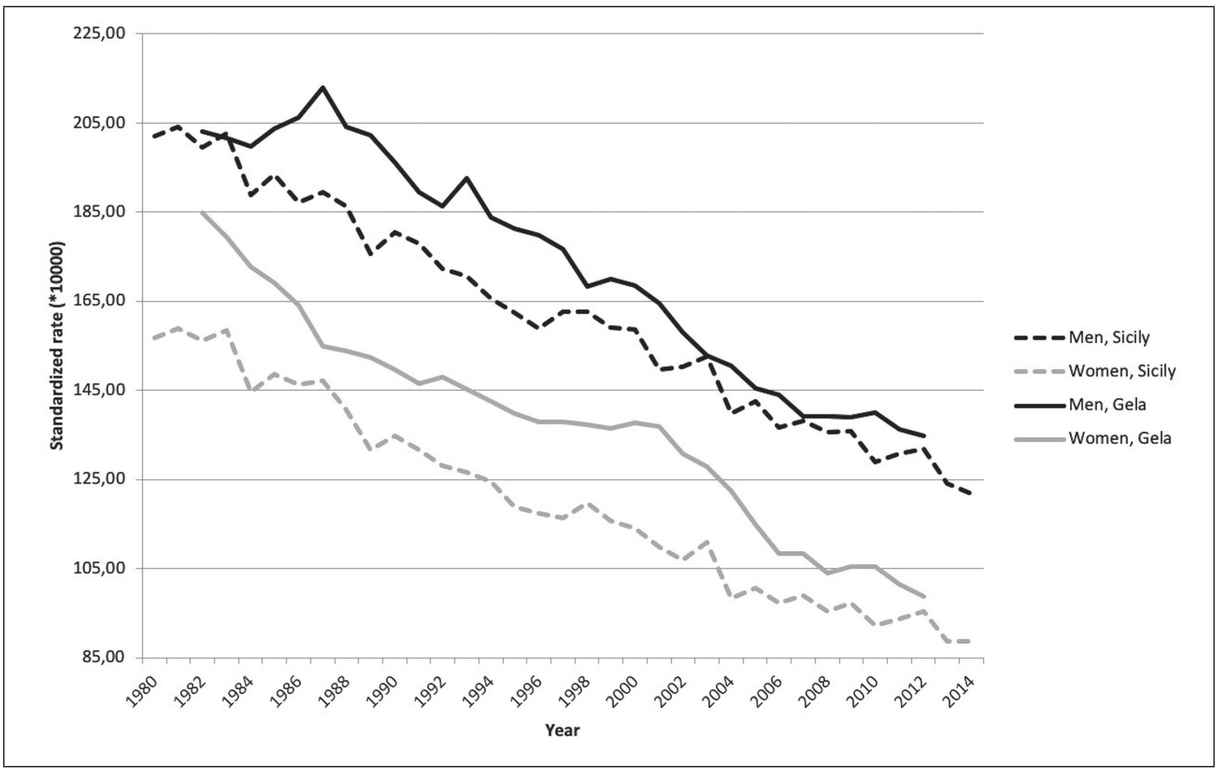

Figure 1
Directly Standardized rates: comparison Gela-Sicily, mortality due to all diseases, both genres, 1980-2014.

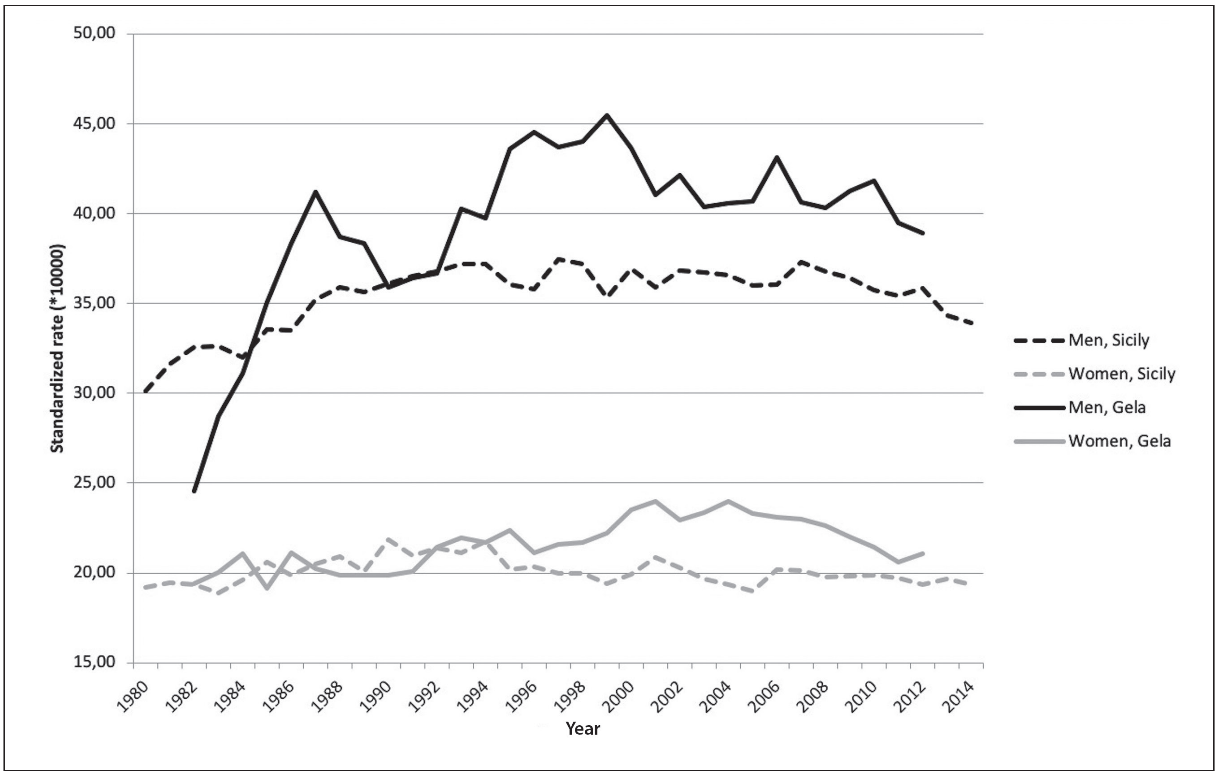

Figure 2
Directly Standardized rates: comparison Gela-Sicily, mortality due to malignant neoplasms, both genders, 1980-2014.

Main results of the Jointpoint analysis are reported in *Table 1*.

SMRs for all diseases, all ages, are almost always higher than one and statistically significant, both for men and women. For men SMRs have values between 1.04 [0.99, 1.09] in the period 1980-1984 and 1.17 [1.12, 1.22] in 1990-1995, since for women lowest value is 1.13 [1.07, 1.19] obtained for the period 1985-1989 and highest one is 1.25 [1.19, 1.31] in the period 2000-2004.

Focusing on mortality due to cancers for all age's men, the profile during the period analyzed is worse than Sicilian one, with SMRs higher than one from 1984 to 2014 with the highest value, 1.22 [1.12, 1.32] in the period 1995-1999. For women, instead, until 1994 values of SMR are lesser than one but since 1995 started to increasing over one until the period 2005-2009 (SMR=1.19 [1.08, 1.30]). Among all malignant cancers, the analysis was focused on the bronchus and lung cancer: for men, an increase of SMR estimates is observed since 1990, 1.00 [0.84, 1.20], until 2004, 1.46 [1.28, 1.67] among all ages. Focusing on results for specific age classes, SMRs in men show risk in excess between 30 and 64 years old in the last period of the study (2000-2014) with an average SMR of 1.36. In absolute terms, in these 15 years, 135 are the observed cases in men vs. the 95 expected. For men of 65+ an SMR of 1.51 [1.28, 1.76] is observed in the period 2000-2004. The SMR trend for women is more fluctuating showing two significant peaks in the periods 1995-1999 and 2005-2009 with values 1.62 [1.14, 2.30] and 1.52 [1.15, 2.00]. For women, the stability of the excess in mortality for circulatory system diseases is observed during all the years analyzed: since the beginning in 1980 until 2009 the values are always higher than 1.20, with confidence interval never contain the unit. Significant excesses in mortality due to genitourinary system diseases are also detected (*Table 2*).

Results of Bayesian analysis show SIRs in men for all the malignant tumours higher than one, but only the

Table 1
Joinpoint regressions, malignant cancer mortality APC, both genders, 1980-2014

	Years	APC	CI (95%)
Men, Gela	1980-1986	9.8**	(3.4 - 24.7)
Women, Gela	1980-2005	0.9*	(0.1 - 1.7)
Men, Sicily	1980-1990	1.8***	(1.3 - 2.2)
Women, Sicily	1980-1990	1.0***	(0.4 - 1.6)

* (P-value <0.05), ** (P-value <0.01), *** (P-value <0.005).

Table 2
SMR for mortality due to all diseases and malignant cancers for men and women, bronchus and lung cancers for men and circulatory system diseases for women, all ages, 1980-2014

	All diseases		Malignant cancers	
	Men (CI 90%) [n. cases]	**Women (CI 90%) [n. cases]**	**Men (CI 90%) [n. cases]**	**Women (CI 90%) [n. cases]**
1980-1984	1.04 (0.99-1.09) [1,239]	1.18* (1.12-1.24) [1,020]	0.90 (0.80-1.01) [201]	1.00 (0.87-1.14) [149]
1985-1989	1.17* (1.12-1.22) [1,383]	1.13* (1.07-1.19) [962]	1.18* (1.07-1.29) [308]	1.00 (0.88-1.14) [165]
1990-1994	1.09* (1.04-1.14) [1,320]	1.17* (1.11-1.23) [1,027]	1.00 (0.92-1.11) [301]	0.98 (0.52-1.48) [184]
1995-1999	1.13* (1.08-1.18) [1,392]	1.18* (1.12-1.24) [1,060]	1.22* (1.12-1.32) [398]	1.11 (0.99-1.24) [221]
2000-2004	1.10* (1.05-1.15) [1,387]	1.25* (1.19-1.31) [1,161]	1.16* (1.07-1.26) [421]	1.18* (1.06-1.30) [261]
2005-2009	1.05* (1.01-1.10) [1,447]	1.20* (1.14-1.24) [1,232]	1.15* (1.07-1.24) [476]	1.19* (1.08-1.30) [306]
2010-2014	1.07* (1.02-1.11) [1,599]	1.14* (1.09-1.20) [1,388]	1.11* (1.03-1.19) [502]	1.09 (1.00-1.20) [327]
	Bronchus and lung cancer, men (CI 90%) [n. cases]		**Circulatory system diseases, women (CI 90%) [n. cases]**	
1980-1984	1.07 (0.87-1.31) [64]		1.25* (1.16-1.34) [524]	
1985-1989	1.06 (0.88-1.28) [79]		1.20* (1.12-1.30) [479]	
1990-1994	1.01 (0.84-1.20) [87]		1.23* (1.14-1.33) [500]	
1995-1999	1.15 (0.99-1.35) [112]		1.22* (1.14-1.32) [508]	
2000-2004	1.46* (1.28-1.67) [154]		1.25* (1.16-1.34) [513]	
2005-2009	1.19* (1.03-1.37) [137]		1.24* (1.15-1.33) [530]	
2010-2014	1.16 * (1.02-1.33) [146]		1.09 * (1.01-1.17) [535]	
	All diseases (age class 45-69)			
	Men (CI 90%) [n. cases]		**Women (CI 90%) [n. cases]**	
1980-1984	1.05 (0.96-1.14) [401]		1.19* (1.07-1.32) [256]	
1985-1989	1.07 (0.99-1.16) [435]		1.12* (1.00-1.24) [244]	
1990-1994	0.99 (0.91-1.07) [422]		1.06 (0.95-1.18) [239]	
1995-1999	1.17* (1.09-1.27) [488]		1.07 (0.96-1.19) [236]	
2000-2004	1.04 (0.96-1.13) [407]		1.11 (0.99-1.23) [231]	
2005-2009	1.08* (1.00 – 1.18) [410]		1.13* (1.02-1.26) [242]	
2010-2014	1.02 (0.94-1.12) [374]		1.13* (1.02-1.26) [256]	

*SMR value statically significant with level of significance of 90%.

stomach and the lung cancers are statistically significant with the highest SIRs (1.08 and 1.07) and 80% credibility intervals that not contain the unit. For women, the highest SIR (1.09 [1.01, 1.20]) is observed for colon cancer. Also for women, the lung cancer presents the second-highest SIR among all sites. The SIR estimates resulting from rank estimates are similar with credibility intervals for different cancer sites overlapped (*Figure 3* and *Figure 4*).

DISCUSSION

Results of the analysis of mortality trends in Gela from 1980 to 2014 show that for all the period analyzed, and for both genders, the SMRs for residents are decreasing but they are higher than those of the Sicilian population by gender, although the gap is decreasing over time. Furthermore, the analysis of rates due to malignant tumours shows that in Gela, for men, the values grew up in the period 1980 to 2000, from 23 deaths/10,000 in 1980 to around 45/10,000 in 2000, then they decreased until reaching the value of 38 at the end of the analyzed period, while for the total of Sicilian men deaths reach a maximum of 37/10,000 in 1997 and in 2014 stands on 34. For women in Gela, the increase in rates was less evident than in men, but it lasted for a longer period: the decreasing trend started only in 2004, ten years after the one observed in Sicilian women. The gap in mortality from all cancers between men and women, especially between 1990 and 2000, could be the result of different risk in the occupational settings. Overall, the results on trends in Gela show an excess of risk, especially in the 1990s and mainly regarding mortality for all cancers.

The results of the SMR analysis suggest that, for both men and women of all ages, deaths in Gela are almost always higher than those observed for Sicily, for general mortality, all malignant tumours, and almost all large groups of diseases (circulatory, respiratory, digestive

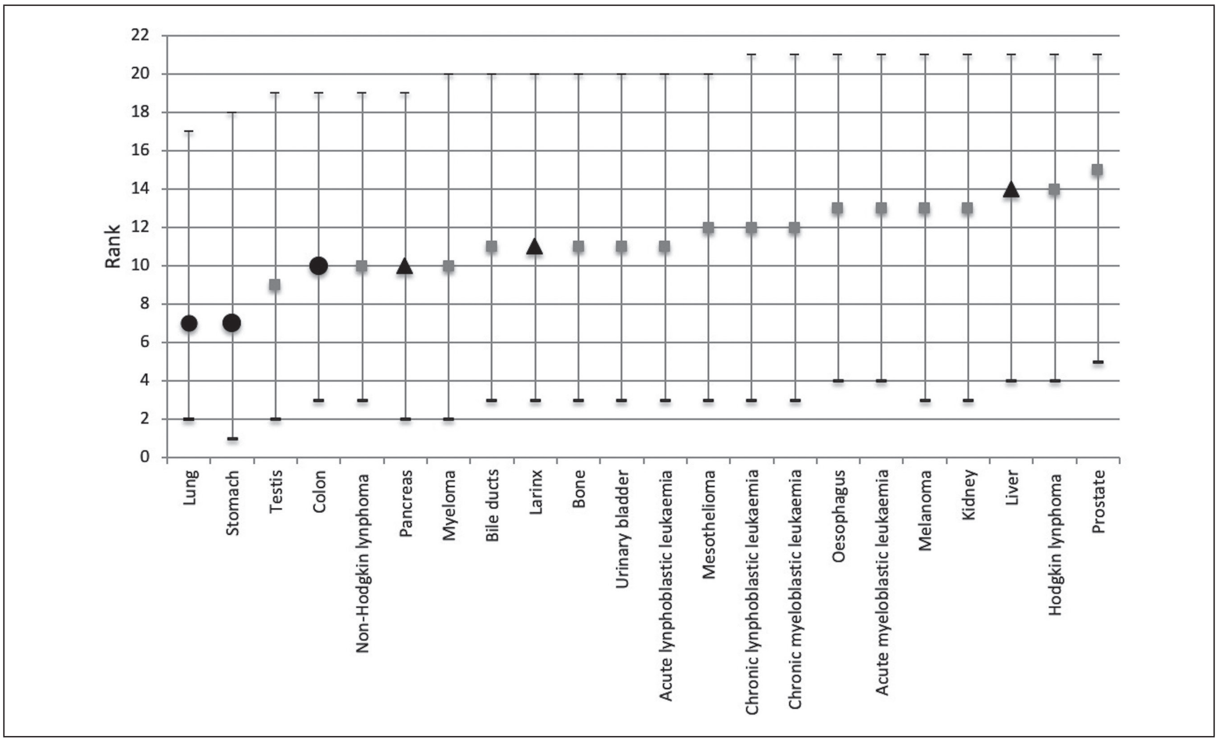

Figure 3
Rank of the neoplasm sites analyzed. *A priori* neoplasms as black circles and control neoplasms as black triangles, for men in Gela.

and genitourinary systems). An excess of mortality for lung cancer, in men in the 45-69 age class, has resulted since 1995. Excesses of mortality due to lung cancer identified are coherent with recent evidence from meta-analysis on risk for populations living close to petrochemical sites [17]. In the systematic revision made by Wong and Raabe limited to the analysis of the risk for workers in petroleum industry (not for the whole populations living close to petrochemical sites) [18] which considered also other outcomes, there were no identified increases in mortality due to digestive, respiratory or genitourinary cancers with meta-SMR estimates below unity.

The results of cancer incidence analysis show excesses of risk for all cancers combined for both genders and for lung and stomach cancer in men. Furthermore, neoplasms of *a priori* interest result as ranked in the first positions for both genders, while neoplasms selected as control are ranked in the subsequent positions. This result, although very weak in terms of statistical significance – credibility interval contain ones and ranks are overlapped, as above mentioned – are initial weak clues on the possible risk associable with petrochemical pollution.

Excesses in cancer incidence for people resident close to a petrochemical complex were identified in several previous studies and meta-analyses. These studies showed that lung cancer incidence, as well as mortality for those who lives near a petrochemical site is significantly higher compared to those who live farther [19, 20] and also the exposure to specific contaminants, mostly emitted from petrochemical complexes is associated to the increases in gastric cancer incidence [21] and leukaemia [22, 23]. Fernandez-Navarro *et al*. (2017) carried out a study in Spain with a design at municipality level analysing possible associations between industrial pollutants emission, estimated using data from the European Pollutant Release and Transfer Register (E-PRTR), and mortality risk for local populations residing in municipalities close to the sites. In a four-year time window (2007-2010), data on pollutants showed high levels of carcinogens also found in Gela's petrochemical site like arsenic, cadmium and chromium. The results of the study regarding cancers showed a mortality risk higher in exposed *vs* non exposed populations especially for pleura and colon-rectum cancers [24].

The notion of disease latency deserves some considerations. This study considered many diseases which could have different latency periods. Diseases associated to chronic exposure to environmental contamination, like cancers, could have long latency periods. The estimated minimum latency period for cancers can range from years to more than a decade [25], while the average latency between the beginning of exposure to cancer onset/diagnosis is usually of decades. For example, the estimated latency between the beginning of active smoking to the incidence of lung cancer was estimated ranging from about 10 to 30 years [26]. Furthermore, the latency period is influenced by several factors beyond the particular chemical or mixture of chemicals considered, including level and duration of exposure. To take this complexity into account in the present ecological study (outcomes available from routinely collected data or data from registries for the whole population without information at individual

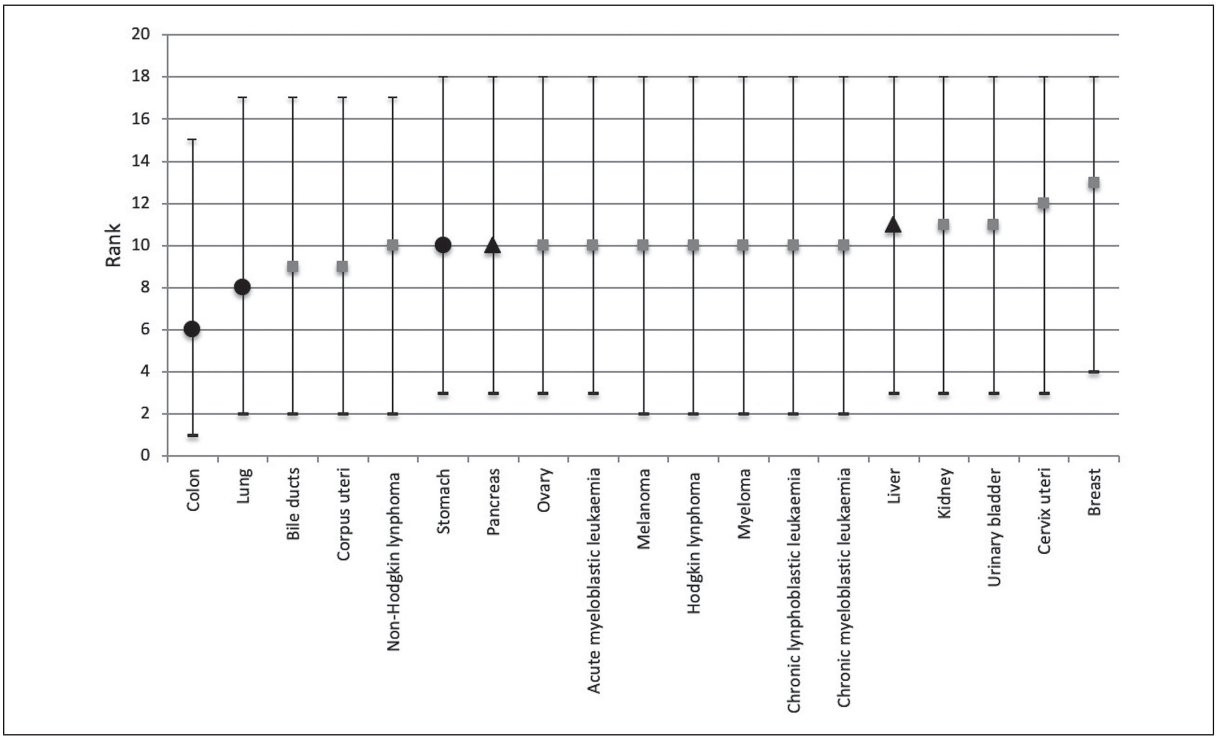

Figure 4
Rank of the neoplasm sites analyzed. *A priori* neoplasms as black circles and control neoplasms as black triangles, for women in Gela.

level), the mortality indicators were computed starting from 1980 (even because this is the first year of mortality data availability), twenty years after the beginning of the petrochemical complex operations (i.e. twenty years after the potential beginning of exposure at least for some contaminants, as for example, those in the air). Furthermore, the selection of the age class 45-69 was made to maximize the difference, during the time window observed, in terms of share of years of life with potential exposure to the pollutants from the petrochemical complex, as described in details in the methods section.

The picture on the risk in Gela resulting from the present study has some limitations. The selection of the Sicilian region population as the reference in the mortality analysis can be questionable, since the difference in risk factors other than the one at study (i.e. the pollution from the petrochemical plant) among the target and the reference population can affect the risk estimates and the inferences in comparing the risk among the populations. The choice of the regional population as reference for the study was pragmatic to balance the need of having quite similar populations in terms of risk and wellbeing factors and to obtain robust analysis in statistical terms also for rare diseases in computing indirect standardized indicators. This option of having the regional population as reference in descriptive epidemiological studies is common in the Italian context and is the one chosen for the SENTIERI monitoring [3].

As described in methods section, the Bayesian model was structured using non-informative prior distributions to give more importance to empirical data. In the case study, before data analysis, there were not specific information about specific diseases compared to others, therefore each cancer site has the same importance into the model. Another option to estimate SIRs would have been to use some informative prior based on, for example, *a priori* cancer sites knowledge, to check if empirical data had confirmed and eventually enlarged the differences between these SIRs and those of the others sites. Furthermore, representation of ranks of SIRs presents some limitations: above all, ranks are computed using SIRs estimated values which were computed having low statistical power due to the short time of data availability of cancer incidence data for the population of Gela (5 years). Nevertheless, the authors chose to present the methodology and describe results as the method applied to the analysis of cancer incidence data is quite innovative for its application to contaminated sites, expecting to provide more robust estimates in the future as longer series of data become available.

The results of this study confirm in general what is presented in the last SENTIERI report regarding the risk in Gela highlighting several excesses of risk in the resident population [3].

CONCLUSIONS

The study aims to evaluate the risk for the population residing in Gela associable with the pollutants available in the contaminated area. All the analyses computed highlight a disadvantage in terms of mortality and cancer incidence of the residents of the municipality of Gela, compared to the Sicilian population. Trends in mortality due to all disease and to malignant cancers, the excesses in mortality highlighted by SMRs and Joinpoint regression, and the excesses of the cancer incidence for all sites, in particular, for those of *a priori* interest, coherently show excess in risk, although for some diseases or neoplasm small numbers do not allow robust estimates.

This study highlights the need to continue the activity of monitoring of the environmental matrices polluted by the petrochemical complex and epidemiological monitoring of the population living in Gela by integrating national and regional approaches [3, 27] with evidence from *ad hoc* studies.

Conflict of interest statement

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

Received on 6 July 2020.
Accepted on 22 March 2021.

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