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The spatial association between environmental pollution and long-term cancer mortality in Italy

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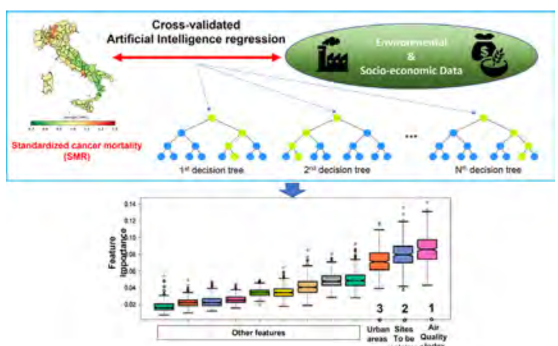
HIGHLIGHTS

- Tumours are nowadays the second world leading cause of death, also in Italy.
- Environmental pollution should be considered one of the main cancer triggers.
- We studied the links between cancer mortality and environmental pollution in Italy.
- Tumor mortality exceeds the national average when environmental pollution is higher.
- Air quality ranks first for importance in relation to the average cancer mortality.

GRAPHICAL ABSTRACT



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ABSTRACT

Tumours are nowadays the second world-leading cause of death after cardiovascular diseases. During the last decades of cancer research, lifestyle and random/genetic factors have been blamed for cancer mortality, with obesity, sedentary habits, alcoholism, and smoking contributing as supposed major causes. However, there is an emerging consensus that environmental pollution should be considered one of the main triggers. Unfortunately, all this preliminary scientific evidence has not always been followed by governments and institutions, which still fail to pursue research on cancer's environmental connections. In this unprecedented national-scale detailed study, we analyzed the links between cancer mortality, socio-economic factors, and sources of environmental pollution in Italy, both at wider regional and finer provincial scales, with an artificial intelligence approach. Overall, we found that cancer mortality does not have a random or spatial distribution and exceeds the national average mainly when environmental pollution is also higher, despite healthier lifestyle habits. Our machine learning analysis of 35 environmental sources of pollution showed that air quality ranks first for importance concerning the average cancer mortality rate, followed by sites to be reclaimed, urban areas, and motor vehicle density. Moreover, other environmental sources of pollution proved to be relevant for the mortality of some specific cancer types. Given these alarming results, we call for a rearrangement of the priority of cancer research and care that sees the reduction and prevention of environmental contamination as a priority action to put in place in the tough struggle against cancer.

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1. Introduction

Almost 180.000 people die every year from cancers in Italy. Although a slightly decreasing trend in northern regions has been observed during the last 20 years and stable mortality in central-southern regions, cancers are nowadays the second world and national leading cause of death after cardiovascular diseases. Breast and lung cancer are the most prevalent forms of neoplasia in women and men, respectively, followed by colon, rectum, prostate, cervix, uterus, stomach, bladder, and other forms. In Italy, lung cancers are causing the highest number of deaths across both sexes (ISTAT 2019).

During the last decades of cancer research, lifestyle and random/genetic factors have been blamed for cancer mortality, with obesity, sedentary habits, alcoholism, and smoking contributing as supposed major causes (Osório-Costa et al., 2009; Khan et al., 2010). Instead, there is an emerging consensus that environmental pollution should be considered one of the main triggers (Bhat et al., 2017; Cazzolla Gatti, 2021). For instance, lung cancer heavily affects also non-smokers: approximately 18,000–27,000 deaths in the world are caused every year by lung cancer in people who are not active cigarette smokers, whose about 20.000 are non-smokers during all life (Thun et al., 2006; Ihsan et al., 2011). Similarly, obesity seems to increase the risk of cancer but does not directly cause it (Deng et al., 2016). Moreover, alcoholism has been identified as a relevant factor in liver cancer induction but it does not represent the only, and it is not the principal, inductor (Cao and Giovannucci, 2016).

Recently, scientific advances have shed more light on this issue: it has emerged that, along with genetic predisposition, incorrect lifestyles, and psychological stressors, exposure to a mix of pollutants, significantly increases the likelihood of developing tumours (Reaves et al., 2015, Kim et al., 2018). Global patterns of cancer incidence and the high number of deaths in the worst-polluted places on Earth serve as unequivocal proof (Blacksmith Institute 2007; Wild et al., 2020). Nonetheless, no place on Earth can be considered completely safe in this era. Higher cancer risks are linked to industrialized countries and workplaces with exposure to chemicals. More than two hundred widely-distribute breast cancer carcinogens have been classified up to now (Rudel et al., 2007; García-Pérez et al., 2016; Rodgers et al., 2018; IARC, 2022) and occupational exposures to specific chemicals showed an increased tumor risk (Hashim and Boffetta, 2014; García-Pérez et al., 2018). There is also clear evidence that most tumours developed by children are highly related to the exposure of parents to carcinogens (O'Leary et al., 1991, Vinson et al., 2011). Researchers started discovering the dangers of indoor pollution initially from domestic chemicals of common use (Hannon and Flaws, 2015, Goncharov et al., 2009, Desdoits-Lethimonier et al., 2012, Steenland and Winquist, 2020, Sjödin et al., 2008, Calafat et al., 2008, Seachrist et al., 2016, Durando et al., 2007, Ho et al., 2006, Snedeker, 2007, Wilson et al., 2007). However, exposure to outdoor chemicals, mainly those employed in intensive agriculture, and pollutants, particularly from industry, is nowadays widely considered one of the main risk factors for human health (Gilliom et al., 2006, Straub et al., 2007, Authman et al., 2015, Quirós-Alcalá et al., 2011).

Besides this scientific evidence, governments and institutions are not financing enough research on the connection between cancer and the environment (Davis, 2007). On the contrary, and besides some sporadic bans, carcinogens in water, air, and soil have continued to accumulate disproportionally and grow in number and dose (Cazzolla Gatti, 2021). In this national scale study, we analyze the links between cancer mortality, socio-economic factors, and sources of environmental pollution at a wider regional and a finer provincial scale in Italy within a robust machine learning framework. To this end, we use the spatial distribution of cancer deaths incidence, expressed as Normalized Mortality Ratio (SMR), available from the SMR DATABASE (Di Paola et al., n.d) which encompasses data at both regional and provincial levels for single cancer categories over the period 2009–2018, along with several socio-economic and environmental variables available from national and regional statistical agencies. Specifically, we outline at a regional scale the existence of general spatial patterns for different socio-economic and environmental drivers, including cancer deaths; then, we focus our attention on a provincial scale to investigate and better understand the association between the mortality for specific cancer types and several sources of environmental pollution.

2. Materials and methods

The main purpose of this study was the investigation of possible significant correlations between the spatial distribution of different sources of pollution and cancer mortality by exploiting standard state-of-the-art machine learning algorithms. To this aim, we considered the available data at two different scales, according to the European Nomenclature of Territorial Units for Statistics (NUTS): (i) Italian Regions (NUTS 1) and Provinces (NUTS 2). At a regional level, several socio-economic indicators are available from the Italian National Institute of Statistics (ISTAT). For this reason, the first level was used for a preliminary consistency analysis that included both socio-economic and pollution indicators, the latter being modeled by a proxy variable Data at the regional scale concern overweight, smoke, available hospital beds, aging, and income (see Section S1 in Supplementary materials).

At the provincial level, several sources of environmental pollution are available from regional agencies for environmental protection, while socio-economic indicators are scarce. Those sources of environmental pollution were evaluated even if, for some of them, the oncogenicity is not definitively proved. Then, a second level was used for a deep assessment of potential spatial associations between cancer distribution and pollution employing Random Forest (RF) (Breiman, 1996) regression coupled with a Boruta feature importance analysis (Kursa and Rudnicki, 2010).

After the evaluation of the RF statistical significance and robustness, we outlined and evaluated the most significant contributions of the available features to cancer mortality. Fig. 1 shows a pictorial representation of the presented analyses. Data on environmental pollutants and sources of pollution include several contaminants of soil, water, and air as well as the presence throughout the provinces of industrial and agricultural activities.

The investigation of the statistical association between cancer mortality and socio-economic or environmental factors is complex and intrinsically influenced by the scale at which the different factors come into action (city, province, region, etc.). This multi-dimensionality makes the analyses extremely challenging; however, the analyses of large samples and the possibility to acquire data representative of large areas can make the analyses more robust. Accordingly, we designed a two-level analysis to fully take advantage of the data available with regional and provincial resolution.

2.1. Data source

2.1.1. Standardized cancer mortality

Data on cancer deaths incidence were retrieved from the Italian SMR Database (Di Paola et al., n.d), which contains the Standardized Mortality Ratio (SMR) for 23 cancer-type macro-categories (Table S1), the broad category of "malignant tumours" (hereinafter cancer type C), and "malignant" plus "non-malignant/uncertain behaviour tumours (hereinafter cancer type C + D), according to the International Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization (WHO). Specifically, the SMR Database holds the SMR estimated over the whole Italian Country for the longest time series analyzed so far, to our knowledge (2009–2018), for three levels of administrative units: municipal, provincial, and regional.

The SMR expresses how much the actual disease incidence for a given locality is close to the expected one, the latter being estimated compared to a reference population (e.g., the national population). Hence, for a given locality, the more the SMR is higher than 1, the more the mortality rate exceeds the expected one (i.e., excess of deaths); on the contrary, the lower the SMR value, the lower the mortality rate (i.e., defect of deaths). In our analysis, we considered the ten-year average of SMR for each administrative unit at both regional (for cancer type C) and provincial scales (23 macro-categories, and the whole cancer types C and C +

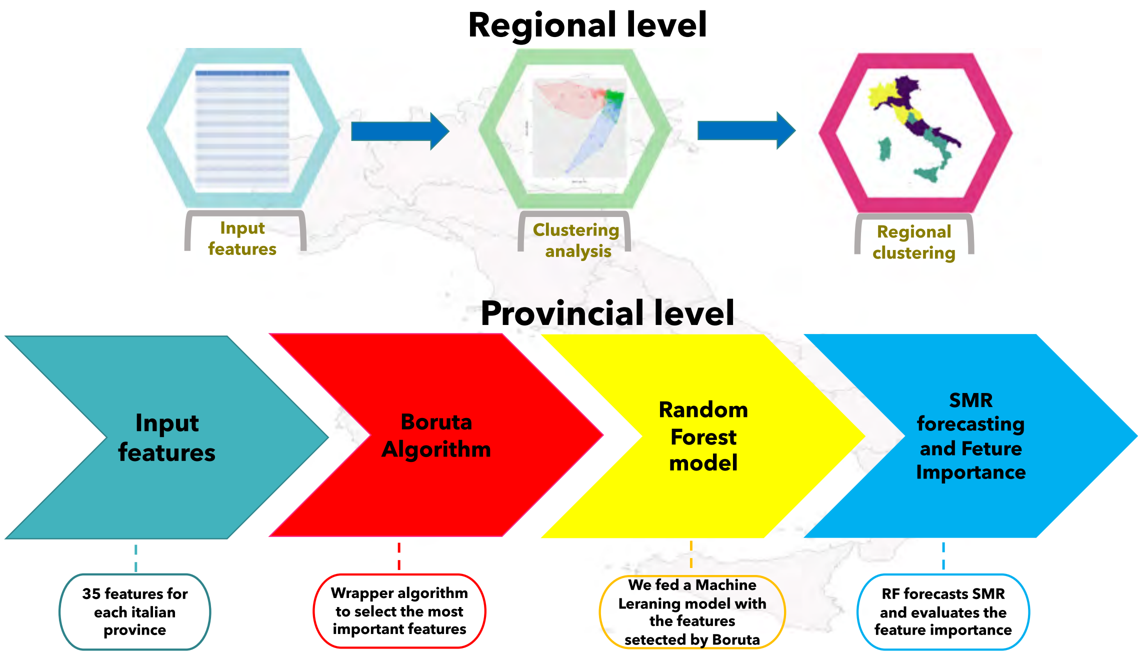

Fig. 1. Conceptual scheme of the proposed analyses. Regional clustering aims at outlining the presence of anomalous patterns for cancer mortality throughout the Italian territory; on the finer provincial scale then the factors driving these patterns are fully examined.

D) to obtain a spatial distribution for comparisons. Figs. S1 provides an overview of average SMR at the regional and provincial scale, respectively, for cancer type C.

Ideally, to maximize data consistency, socio-economic and environmental variables should be estimated by averaging data over the same SMR data period (2009–2018). However, this is not always possible since most of these variables are not monitored every year. Since the proposed research looks for possible spatial correlations between cancer mortality and environmental pollution, the collection of the input variables is mostly aimed at having the most complete and representative spatial data, acknowledging some possible temporal inconsistency, and assuming that there have been no substantial changes in the spatial distributions of pollutants over the decade considered.

2.1.2. Regional features

At a regional scale, we took into consideration some socioeconomic and lifestyle variables to compare them with the "proxy pollution", a summary feature expressing the broad degree of the effects of pollution on cancer mortality.

We called "Overweight" the average percentage of subjects by Italian region in excess weight (overweight and obese subjects) provided by the epidemiological information portal (EpiCentro) of the Italian National Institute of Health (2021). With "Overweight" we mean people with a body mass index (BMI) between 25 and 20 (while people with BMI 30 are included in the "obese" group).

We defined as "Smokers" the average percentage of smokers in each Italian region extracted from Epicentro (2021). Smokers are the subjects who have smoked 100 or more cigarettes in their life and were continuing to smoke at the time of the survey.

We indicated as "Hospital beds" the average number of beds in public hospitals, per regional population provided by the Italian Ministry of Health (2019).

We defined as the "Old-age index" the average ratio between the population aged 65 years and over and that under 15 in each Italian region, extracted provided by the National Institute of Statistic (ISTAT) from published in ISTAT (2019).

We called "Income" the mean annual income per family extracted by the System of Regional and Provincial Social Indicators of the Institute of Economic and Social Research of Piedmont (2021).

ISTAT (https://www.istat.it/en/) also collects data on the eating habits of Italians. In particular, we selected the following variables:

- As "Fruit and vegetable consumption" the percentage of subjects in the Italian regions who declare that they eat fruit or vegetables at least once a day;
- Six features concerning the consumption of animal-source food meats, defined as the percentage of subjects in the Italian regions who declare that they consume cured meats, white meats, beef, pork, eggs, and fish more than once a week.

We summarized the six variables on animal-source food into a single feature ("Meat consumption"), namely the first component resulting from a Principal Component Analysis (PCA; Jackson (1991)). Principal component analysis (PCA) can describe with a good approximation the information contained in a dataset using a small number of principal components (PCs). PCs are made as a linear combination, orthogonal to each other, of the dataset features; the first principal component PC1 represents a large fraction of variation (variance explained) in the sample, and successive PCs account for decreasing portions of the remaining variation. Therefore, to get a good representation of the data we can use only the first few PCs because the lower higher-order ones contain redundant information or noise.

In our analysis, to build the feature "Meat consumption" described in Section 2.2.2, we considered only PC1, which contained almost 80 % of the data variance.

Finally, we called "Proxy pollution" a summary feature expressing the broad degree of the effects of pollution on cancer type C. This variable is the output of an RF model trained at the provincial level (hence only with environmental features), whose outcomes were aggregated at the regional scale, and can be considered a summary value of the average pollutant levels from the provincial sources.

2.1.3. Provincial features

We managed to collect 35 variables as sources of pollution at the provincial level. In particular, we took into account direct pollution sources such as the use of nitrogen fertilizers or arsenic and other variables which are suitable proxies such as the vehicle density or the Air Quality Index. The goal was to provide an accurate picture of the pollution sources as well as include in the model the widest base of knowledge; to this aim, we also included some variables characterizing the presence of specific transport infrastructures (such as roads, airports), agriculture and factory activities particularly related to the pollutants' production (such as mines or refineries).

The full list of such input variables, along with descriptions and related data sources, is presented in Table S2.

2.2. Regional cluster analysis and provincial Random Forest

2.2.1. K-means clustering

Italy counts 20 territorial units at regional level (i.e., NUT2). To look for likely relationship within the data without any prior assumption while dealing with such a sample size we opted for a K-means cluster analysis (Jain, 1988). This analysis provides information on where associations and patterns in data exist. Specifically, in our study, we adopted the k-means clustering algorithm to explore the possible spatial association between environmental pollution, socio-economic factors, and the whole cancer deaths incidence. The K-means algorithm was implemented for regional analysis using as independent variables the features described in Sections 2.1.2 and 2.1.3. Pairwise Pearson correlation tests among the variables were also carried out to allow a better interpretation of the results. Details on K-means algorithm and implementation are provided in the section SM1 of the Supplementary materials.

2.2.2. Random Forest

At the time of writing, Italy counted 107 provinces. At this spatial scale, the size of data (i.e. 107 data for each variable) allowed us to use a machine learning algorithm to model the SMR. Specifically, at first, we used the Boruta algorithm, a wrapper method, to select the most important features among those reported in Section 2.1.2; then we implemented a Random Forest algorithm, fed through the features chosen by Boruta, to model the SMR index for each macro-categories of cancer listed in Table S1, including the broad categories C and C + D. Details on Boruta and Random Forest algorithms and implantation are provided in the section SM2 of the Supplementary materials.

3. Results

3.1. Regional cluster analysis

The regional cluster analysis performed over 7 environmental and socio-economic variables suggested 3 clusters of regions (Fig. 2), with a maximum value of silhouette equal to 0.4, as the optimal outcome.

The clusters do not show either a well-defined spatial pattern (for example according to latitude) or a completely random one. In Cluster 1 northern, central, and southern regions are quasi-randomly distributed, Cluster 2 embraces islands and mostly Tyrrhenian central-southern regions, whereas Cluster 3 includes central-northern regions mostly on the western side of the Country.

The K-means analysis revealed that regions in Cluster 2 (orange group in Fig. 2) have a relatively low incidence of cancer and, at the same time, a relatively low environmental pollution and income. Yet a relatively high number of overweight people and smokers, and high meat consumption is recorded in this cluster. By contrast, regions in Cluster 3 (green group in Fig. 2) have a relatively high cancer deaths incidence despite having all the characteristics that theoretically should keep cancer levels low except for environmental pollution: a relatively low number of overweight and smokers, low meat consumption, high fruit and vegetable consumption, and high income. Regions in Cluster 1 (blue group in Fig. 2) show similar socio-economic and mortality values to those in Cluster 3 except for the lower number of overweight and smokers.

Among all the variables analyzed, environmental pollution is higher when SMR is also higher (Fig. 2). Given such a result showing the potential role of the source of environmental pollution in determining a high cancer death incidence, we proceeded with a finer provincial scale analysis of the potential links between several sources of environmental pollution and cancer mortality.

3.2. Provincial scale assessment

At the provincial scale, we found higher SMR (as the ten-year average of malignant tumours) in central-northern provinces compared to southern ones (Fig. 1a and Supplementary Fig. 1), consistently with the regional outcomes. The province of Lodi ranks first in terms of mortality by malignant cancers out of 107 Italian provinces, followed by those of Napoli, Bergamo, Pavia, Sondrio, Cremona, Gorizia, Caserta, Brescia, and Piacenza among the first ten (Supplementary Table 3). Among the 35 environmental variables considered (Fig. 1b and Supplementary Table 2), the Boruta approach suggests that 12 of them are significantly important in explaining cancer deaths incidence, namely AQI, sites to be reclaimed, urban areas, vehicle density, cultivated areas, AIAU, kilometres of roads, herbicides, IPA, CTE, chemical industries, and landfills (Fig. 3c). The more detailed Random Forest analysis, fed by these pre-selected variables, shows that the AQI ranks first for importance concerning the average cancer mortality rate in Italian provinces, followed by other three main features: sites to be reclaimed, urban areas and vehicle density (Fig. 3d). Besides the first 4, other 8 out of 35 environmental variables (namely, cultivated areas, AIAU, kilometres of roads, herbicides, IPA, CTE, chemical industries, and landfills) proved to be relevant environmental sources of pollution concerning the overall cancer mortality of Italian provinces.

16 out of 23 macro-categories of cancer resulted significantly associated with the proposed model and the considered sources of environmental pollution (p-value <0.01 Bonferroni correction, Supplementary Fig. 2). Among these, the variability explained by the RF model using only the sources of environmental pollution related features ranges approximately between 30 and 50 % ($R^2 = 0.3$–0.5) for 11 categories, 15–30 % for 5 categories. 7 categories show no significant spatial association (i.e. larynx, colon, rectus and anus, thyroid, cervix uteri, leukaemia, other malignant tumours of the lymphatic/hematopoietic tissue, and non-malignant tumours). Pancreas, breast, and kidney tumours show the highest grade of association with the sources of environmental pollution ($R^2 = 0.5$, Supplementary Fig. 2).

Of the 16 tumours significantly associated with the environmental pollution sources, cultivated areas show to be the most important environmental factor for RF in determining cancer deaths incidence for “lips, oral cavity, pharynx”, “liver and intrahepatic bile ducts”, and “esophagus” tumours (with AQI, herbicides, and fungicides also playing an important role) and the second most important (after IPA) for stomach cancers (Fig. 4). AQI is the main factor in pancreas cancer mortality, with additional industrial activities in urban areas in second place, and the second most relevant pollutant for “liver and intrahepatic bile ducts” and “esophagus” (Fig. 4). Urban areas are the most important source of pollution linked to the trachea, bronchi and lung cancers, and breast tumours. Sites to be reclaimed rank first among the important variables for RF in skin melanoma, brain and CNS, and ovary tumours (Fig. 4). Sites to be reclaimed resulted in a very important feature also for kidneys and Hodgkin and lymphomas mortality, second to AIAU (Fig. 4).

TV and Radiofrequency emitters, followed by steelworks and PPVAI, show the highest ranks in the bladder tumours (Fig. 4). Steelworks is the most associated variable with cancers on other parts of the uterus, while kilometres of roads with all other malignant tumours (Fig. 4).

Overall, in some cancer types - such as those in prostate, bladder, and breast - the number of significant variables output from RF is relatively high and, among these, at least 3 variables rank among the most important ones (Fig. 4). By contrast, in other cancer types such as stomach, brain and CNS, and other parts of the uterus only a few variables resulted as significant for RF (Fig. 4).

Again, some sources of pollution are widely present in the machine learning outputs such as AIAU, AQI, cultivated areas, sites to be reclaimed, steelworks, and urban areas, above all (Supplementary Figs. 3 and 4).

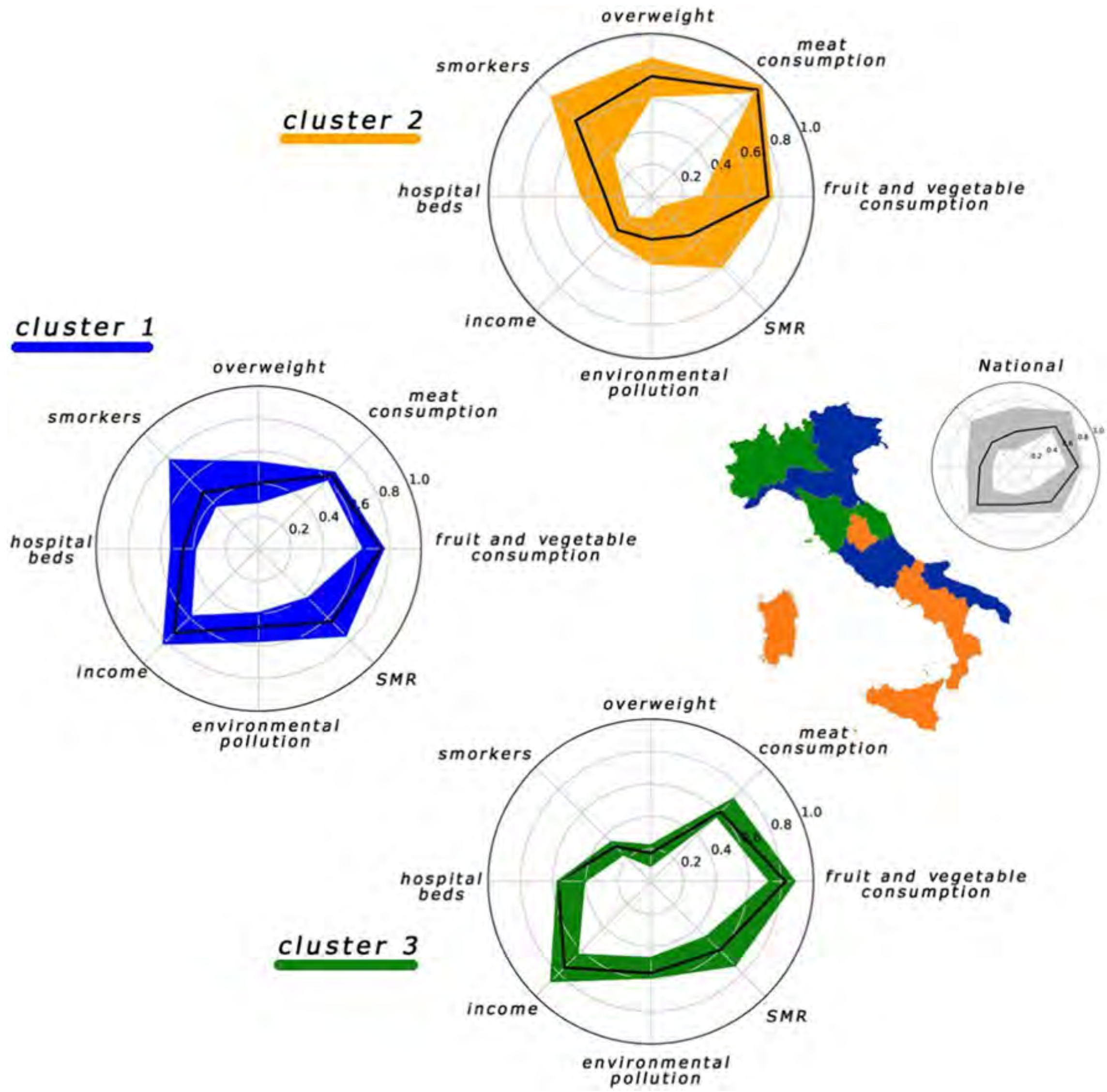

Fig. 2. Regional clusters from socio-economic and environmental variables. SMR refers to cancer type C. In the radar graphs: black lines are the median, filled coloured areas that embrace the 25-75th percentile range. Values were normalized in the range 0–1 to aid data comparison.

4. Discussion

Our findings, besides providing solid support to most of the previous studies, expand the current knowledge on the burden of sources of environmental pollution on cancer mortality. With a hierarchical multi-scale approach we were able to, firstly at a bigger national and regional scale, show the relevance of the environment compared to other socio-economic and lifestyle factors, and secondly determine, at a finer provincial scale, potential sources of pollution likely causing an excess of cancer deaths from the expected average, and finally provide a focus on the to the environmental factors that are mostly associated with specific cancer types.

We firstly found that, in Italian regions, there are neither spatial nor random patterns of cancer mortality distribution. This finding may provide more support to the idea that random factors (often associated by people with luck and misfortune) are not the major triggers of tumours, contrary to what has been suggested so far (Tomasetti et al., 2017).

Specifically, two major results emerged: *i*) at the regional scale, regions having a relatively high rate of cancer mortality are characterized by a relatively high degree of pollution although a relatively low incidence of factors generally associated with cancer risk (i.e., overweight people and smokers, low income, high meat, and low fruit/vegetable consumption); *ii*) at the provincial scale, the broad category of malignant and benign cancers and 16 out of 23 specific cancer types showed a significant spatial association (which explain more than half the association with tumours), confirming that, in most cases, the exposure to environmental pollution in Italy does affect the cancer mortality, in contrast to what has been claimed with previous studies in other countries (e.g. Boffetta et al., 2009). However, we are aware that a higher cancer death rate in some highly polluted regions is not completely unlinked to smoking habits, particularly when combined with overweight. These combinations can still represent the most likely cause of cancer deaths. Nonetheless, the lack of clear knowledge of the interactions between lifestyle factors and environmental pollution, which increase cancer mortality, prevents a definitive understanding of the causality, at the moment.

4.1. Regional clusters of socio-economic and environmental pollution

The regional cluster analysis, performed by using both socio-economic and environmental variables, does not show well-defined spatial patterns of cancer death incidence in Italy, albeit some neighbouring regions were classified in the same cluster. What clearly emerged, instead, is that regions having a relatively low rate of cancer mortality showed a relatively high incidence of factors generally associated with cancer risk (i.e., overweight

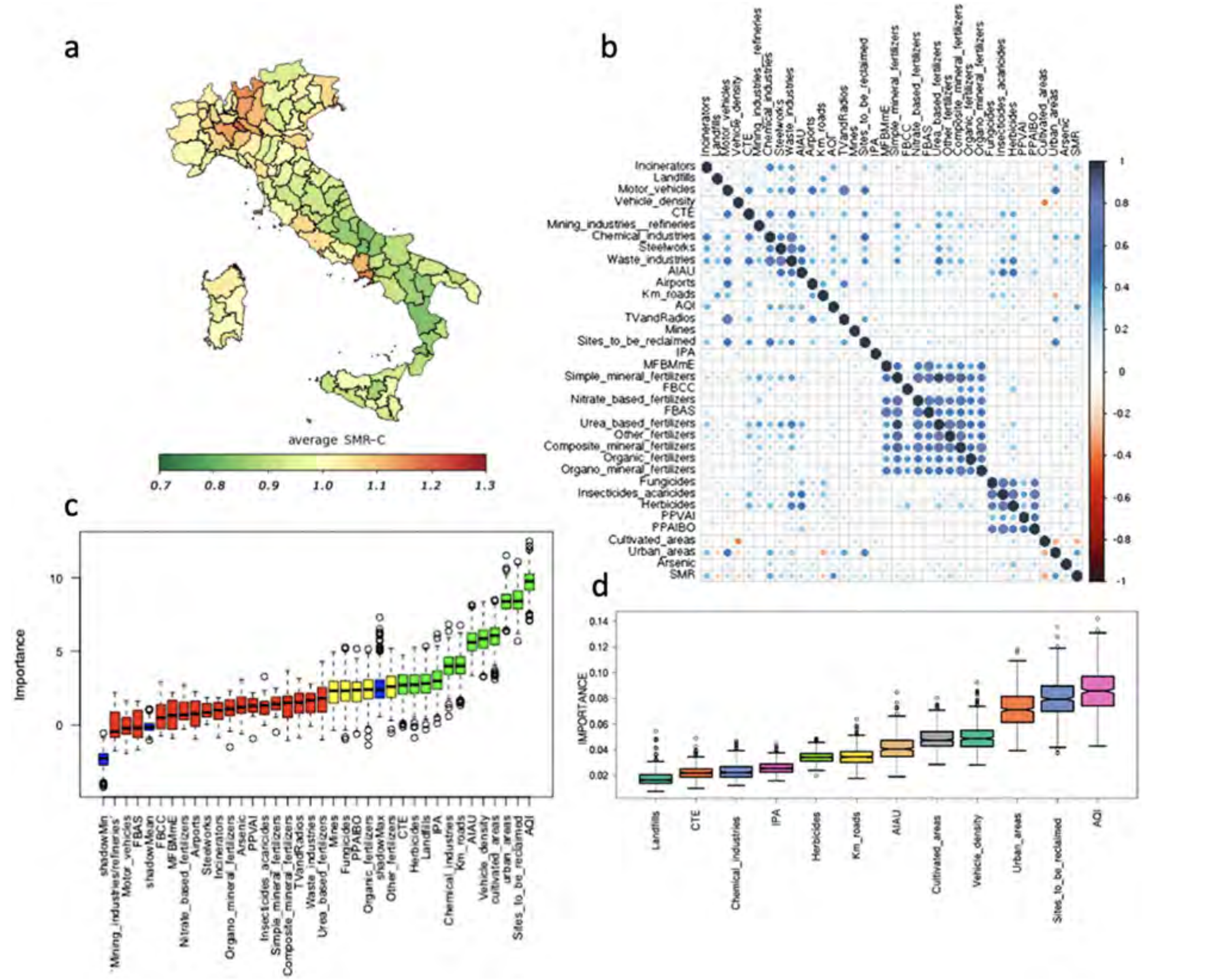

Fig. 3. a) Average standardized mortality rate (SMR for malignant tumours) distribution within Italian provinces; b) correlogram of environmental variables; c) feature importance for all cancers mortality (c) Boruta and (d) Random Forest.

people and smokers, low income, high meat, and low fruit/vegetable consumption). This would appear as a counterintuitive result because it is well known that a good lifestyle can reduce cancer incidence (Wang et al., 2021). However, this finding is not necessarily in contrast: healthy life habits such as the quality of food, physical fitness, diets, and access to medical care are purely individual choices while environmental pollution exposes the whole population to diffuse toxicity. In this sense, in polluted environments, there may be high cancer deaths in people with unhealthy lifestyles, and/or it may be that healthier lifestyles are unable to counterbalance the triggering effects for tumours of a life spent in areas with a high concentration of pollutants. Hence, we found good, although preliminary, clues that a better lifestyle and more care for socio-economic and health issues can reduce only partially the risk of dying of cancer in the whole population if the quality of the living environment is undervalued. Yet, the death toll for tumours can even be higher than that of citizens not caring much for their health but living in less polluted places. This, in turn, could explain the reason why we observed that people living in Northern regions of Italy (particularly those located in the heavily industrialized Po Valley) and exposed to very high environmental pollution levels show significant excess mortality for cancer compared to the living people in the Southern regions, even though better health (fewer smokers and overweight people), higher income, bigger consumption of plant-based food compared to animal-based one, and easier accessibility to healthcare.

4.2. Provincial environmental pollution and mortality for single cancer categories

Potential spatial association among several sources of environmental pollution and specific cancer type mortality emerged at a finer provincial scale with the help of machine learning. Overall, we found that air pollution (AQI), cultivated and urban areas, and other industrial activities in urban areas are among the most important factors associated with high cancer mortality. This trigger of tumours is followed, in order of relevance, by highly contaminated sites (to be reclaimed), urban and agricultural areas extent, motor vehicle density, industrial activities in urban areas, exposure to pesticides and allergenic pollens, and presence of chemical sites, energy plants, and landfills nearby.

It is not surprising that the heavy contamination in the air (but also likely in soil and water) of urbanized areas, particularly those close to polluting industrial plants and surrounded by intensive agriculture exacerbates the risk of contracting and dying from a tumor. Indeed, our results are in agreement with the growing evidence in the literature that agricultural, industrial, urban, chemical, and waste pollution which, mainly, affects the quality of air (and, often consequently, of soil and water) is linked to several types of tumours (Boffetta, 2006; Kampa and Castanas, 2008).

From the analysis of the contribution of environmental pollution sources to the mortality for specific cancer types, some general patterns emerged.

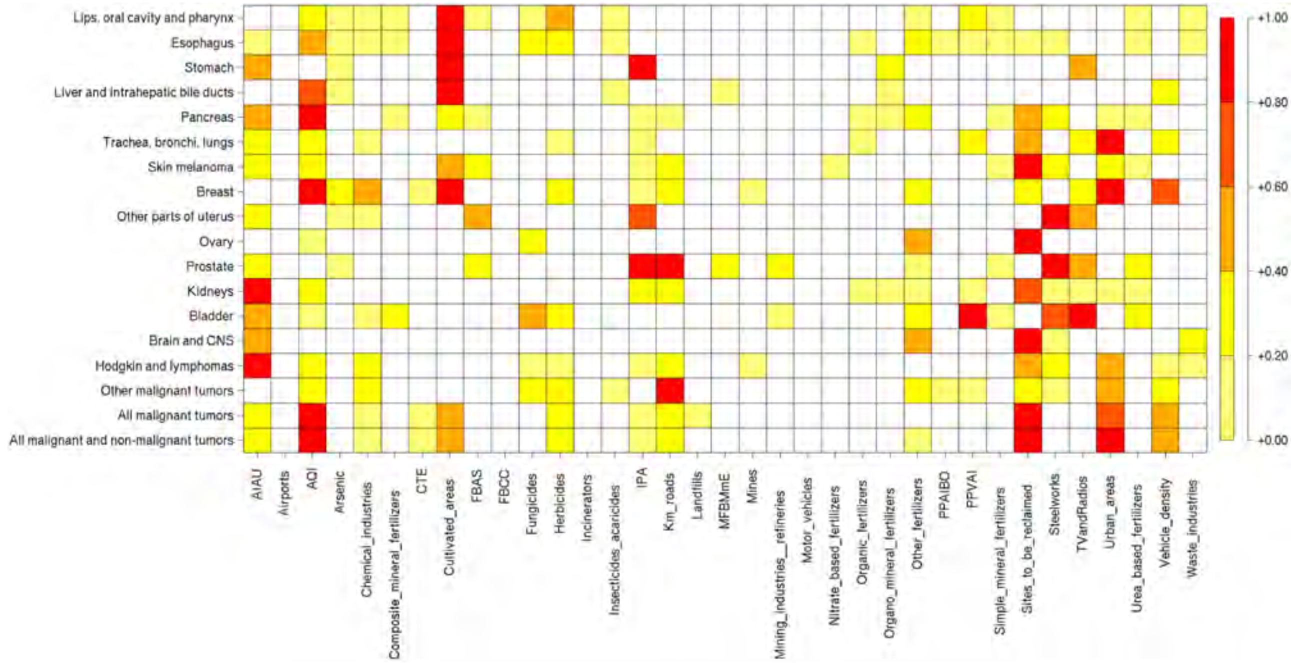

Fig. 4. The most frequent sources of pollution (averaged values; for their variability see Supplementary Figs. 3 and 4) are revealed by machine learning according to Random Forest variable importance analysis for cancer mortality. The white boxes indicate that the corresponding variable was not important for the preselection by Boruta.

Air quality, the extent of cultivated areas, use of pesticides, exposure to allergenic pollen, and presence of industrial sites in urban areas result strongly related to tumours of the gastrointestinal system (which includes the mouth, liver, pancreas, stomach, etc.). Our finding could be related to the evidence, both in human and laboratory studies, that dioxin - a co-product, together with polycyclic aromatic hydrocarbons, of incomplete combustions - can induce liver cancer (Tritscher et al., 1992). Dioxin is one of the most dangerous products of many industrial activities and accumulates in the environment (Fierens et al., 2003; García-Pérez et al., 2021). Interestingly, allergenic pollen and cultivated areas resulted to be the most important factors for stomach cancer mortality from our data. Recent evidence showed that air pollution affects asthma and allergic rhinitis because particulate and gaseous pollution drives pro-allergic inflammation through the generation of oxidative stress, which is regulated by individual genetic susceptibility (Saxon and Diaz-Sanchez, 2005). It is well known the gatekeeping function of the stomach in the sensitization and effector phase of food allergy (Untersmayr and Jensen-Jarolim, 2008). The human immune system elicits both innate and adaptive immune responses against external elements such as pollens and pathogens including oxidative stress (Tsugawa and Suzuki, 2021). Recent attention focused on the relationship between oxidative stress and cancer (Sosa et al., 2013) and this might explain why we found that pollen and cultivated areas are the most important factors for stomach cancer mortality in our analysis. However, more investigation into this association is needed to clarify the strength of these links.

We also found that the extent of urban areas is linked with the respiratory system (trachea, bronchi, lungs) tumours. It is well known that the presence of hydrocarbons, volatile organic compounds, and sunlight form photochemical smog, with secondary pollutants such as peroxyacetyl nitrates (PANs). These substances are considered “urban factors” in triggering lung cancer (Cohen, 2000; Vineis and Husgafvel-Pursiainen, 2005; Clapp et al., 2008; Chen et al., 2016).

Heavily polluted sites (to be reclaimed) showed to be more associated with the epidermal and nervous systems (skin, brain, CNS) cancers. Previous studies reported that municipalities characterized by the highest levels of petrochemical pollution and fine particulate matter (PM) had a statistically significant higher risk of developing skin and brain cancer (Liu et al., 2008; Kim et al., 2016; Poulsen et al., 2020). However, the majority of studies analyzed the effects of air pollution on skin and brain cancers, whereas we found that sites to be reclaimed because of their high level of contamination have a stronger link with these tumours. Therefore, more investigation may be needed to assess all the possible sources of pollution that can trigger skin and brain cancers.

For the urinary system (bladder, kidney, prostate) tumours, steelworks reveal to be a common source, whereas allergenic pollens, roads extent, sites to be reclaimed, and industrial activities in urban areas also emerged to be important. It is interesting to notice that the presence of TV and radio frequency emitters, and exposure to pesticides seem key factors for bladder mortality and are also quite important in prostate cancer. It has been documented that living near high-traffic areas and industries increases the risk of bladder cancers (Yeh et al., 2017; Sakhvidi et al., 2020). Moreover, jet fuels, which release a mixture of nitrotoluenes, fine particles, and other pollutants in exhaust fuels, is considered a probable source of carcinogen because it is linked to liver cancer (Kim et al., 2014). Similarly, there is a long history of studies about the link between synthetic dyes and bladder cancer among textile workers and higher bladder cancer risk for workers in rubber and metal industries (NIOSH, 1980; Monson and Nakano, 1976; Cole et al., 1972; Vineis and Di Prima, 1983). Although they can naturally be elements of some soils, chromium, and arsenic, which can have high levels in industrially contaminated groundwaters, are of serious concern for bladder, prostate, and kidney cancer induction (Zhitkovich, 2011; Bulka et al., 2016; Roh et al., 2017). Illegal disposal of garbage and even legal landfills are another source of carcinogens' percolation and soil contamination and increase the risk of bladder and prostate cancer when populations are exposed to illegal dumping of toxic wastes and their burning (Di Lorenzo et al., 2015; Rocco, 2016).

Most of the dissemination of aromatic amines has been through pesticides in agriculture, although they are a wide group of chemicals that include ingredients in tobacco smoke. Several aromatic amines have resulted in a connection with bladder cancer, which is common among farmers (Koutros et al., 2009). Bladder cancer is also linked to air pollution, with a strong association with mortality among people living in residential districts polluted by industrial petrochemical plants (Pan et al., 1994; Trichopoulos and Petridou, 1994; Liu et al., 2009; Tsai et al., 2009). Among other suspected carcinogens in the soil, nitrates, which accumulate after over-fertilisation in agricultural products and leach in aquifers, may increase the risk of bladder cancer (Ward et al., 2003; Grosse et al., 2006; Jones et al., 2016).

TV and Radiofrequency, which include the radio and television installations and radio-base antennas (also as signal repeaters for mobile phones) monitored by the public authorities as sources of non-ionizing radiation, emerged as an important factor in the cancer of the bladder, prostate, and other parts of the uterus. However, previous research does not show any clear evidence of a direct link between TV and radio emitters of non-ionizing emissions and cancer (Gupta et al., 2022), and studies claiming an association are a few and limited to specific experimental exposures (Satta et al., 2018; Falcioni et al., 2018). Although this correlation is unclear, we suggest that further investigations on cancer development and death linked to TV and Radiofrequency emitters are still needed, also because they can represent comorbidity causes.

Women's reproductive system (ovary, uterus, and breast) cancers seem not linked to a specific, most relevant cause, while a combination of factors such as air quality, urban and agricultural areas, vehicle density, presence of sites to be reclaimed, chemical industries, and steelworks, exposure to allergenic pollens and fertilizers seems to importantly contribute to these tumours mortality. Our findings confirm previous evidence that carcinogens in the air do not only trigger lung cancers but are documented risk factors (Brody et al., 2007), as well as the residence near industries and high traffic areas for breast cancers (Hystad et al., 2015; White et al., 2018), also because aromatic hydrocarbons, like the benzo[*a*]pyrene, which are emitted by the combustion of coal and petroleum derivatives, are involved in the DNA mutagenesis of the mammary gland cells (Korsh et al., 2015). Furthermore, chemical components of some pesticides are proven endocrine disruptors, which affect the hypothalamic control of pituitary-ovarian function (Cooper et al., 2000) and trigger human ovarian cancers (Young et al., 2005; Freeman et al., 2011; Inoue-Choi et al., 2016).

Finally, the extent of roads emerged as the main factor linked to other, rarer, malignant tumours. Among air pollutants that may act as carcinogens from heavily-trafficked roads, ultrafine particles are of higher concern because of their ability to penetrate deeply into the respiratory system (Buonanno et al., 2015; Cazzolla Gatti et al., 2020).

We acknowledge that our study has some limitations. The first one is data availability, which affects the specification of proper features to be used to feed machine learning algorithms. For instance, the absence of socio-economic variables at the provincial scale prevented us from making a comprehensive analysis including and comparing both the socio-economic and environmental factors. Furthermore, at the provincial scale, some sources of pollution, potentially determinants of cancer risk, are unavailable, such as, for instance, radon and arsenic in water). This is particularly relevant since it limits the specification of input variables, which in turn, is one of the most relevant key successes for a performing machine learning algorithm. Last but not least, we cannot account for social stochastic phenomena like immigration-emigration from the place of residence, which could slightly affect mortality rates. Overall, such shortcomings might explain, at the same time, why some cancer categories do not reveal any spatial association with the sources of environmental pollution despite the large number of variables explored and the use of a machine learning algorithm. Or, vice versa, this might suggest that some specific tumours types are not mainly related to the environment or that potentially better results may be achieved.

Additionally, some punctual sources of pollution that do not show relations with any specific cancer type (e.g. incinerators, airports, etc.) may still be linked to mortality at a more local level (i.e. municipal), but could not be revealed by analyses at regional and provincial scales.

A future approach, despite the lack of punctual pollution data (at the local level), might consider the clustering of mortality rates at the municipal scale to reveal hotspots of potential environmental concerns.

Nevertheless, to our knowledge, our analysis represents the most comprehensive assessment of the interconnections between environmental and health factors affecting a whole Italian population, carried out with a wider set of variables and with the support of artificial intelligence so far.

Our study does not dispute that a healthier lifestyle helps reduce the risks of cancer as well as does not challenge the efforts to understand the genetic basis of cancer. Rather, our findings give us good reasons to believe that living in, or closer to, a highly polluted place could overcome the benefits of better life habits and induce, with higher frequency (which ultimately leads to higher mortality), cancer in people with a genetic predisposition.

We, therefore, call for a stronger recognition of the link between exposure to environmental pollution and cancer and we highlight the need for a more "One Health approach" in epidemiology because only with the development of multi and interdisciplinary undertakings (e.g. new Centers for Environmental Health) we could be able to reduce our impacts on the environment and, at the same time, our death toll from cancers.

5. Conclusion

In a nutshell, we explored the potential spatial association between socioeconomic and lifestyle factors, many sources of environmental pollutants, and cancer mortality in Italy. Some environmental factors have repeatedly shown their relevance to deaths for multiple forms of cancers. With the findings that emerged from this study, we call for a reconsideration of the priority of cancer research and care that sees the reduction and prevention of environmental contamination as one of the main priority actions to put in place in the tough struggle against tumours. We acknowledge that diet, obesity, and infections are key factors too, and in many cases, these are not related to individual actions but the social class and poverty. However, the genes we inherit and the lifestyle we decide or are forced to adopt may be the sliding doors of a station towards either sickness or wellness, but the quality of the environment we live in is the train where we will spend the journey. If the coach is polluted, our efforts for a comfortable trip could be fruitless (even literally!).

CRediT authorship contribution statement

Roberto Cazzolla Gatti: Conceptualization, Resources, Validation, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Arianna Di Paola:** Conceptualization, Resources, Validation, Data curation, Formal analysis, Investigation, Writing – review & editing. **Alfonso Monaco:** Conceptualization, Resources, Validation, Data curation, Formal analysis, Investigation, Writing – review & editing. **Alena Velichevskaya:** Resources, Validation, Writing – review & editing. **Nicola Amoroso:** Conceptualization, Resources, Validation, Data curation, Formal analysis, Investigation, Writing – review & editing. **Roberto Bellotti:** Resources, Validation, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.158439.

References

Authman, M.M., Zaki, M.S., Khallaf, E.A., Abbas, H.H., 2015. Use of fish as bio-indicator of the effects of heavy metals pollution. J. Aquaculture Res. Dev. 6 (4), 1–13.

Bhat, S.A., Hassan, T., Majid, S., Ashraf, R., Kuchy, S., 2017. Environmental pollution as causative agent for cancer-a review. Cancer Clin. Res. Rep. 1 (3), 1–8.

Boffetta, P., 2006. Human cancer from environmental pollutants: the epidemiological evidence. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 608 (2), 157–162.
Boffetta, P., Tubiana, M., Hill, C., Boniol, M., Aurengo, A., Masse, R., Valleron, A.-J., Monier, R., de Thé, G., Boyle, P., Autier, P., 2009. The causes of cancer in France. Ann. Oncol. 20 (3), 550–555.
Breiman, L., 1996. Bagging predictors. Machine Learning. Volume 24. Springer, Berlin/ Heidelberg, Germany, pp. 123–140.
Brody, J.G., Moysich, K.B., Humblet, O., Attfield, K.R., Beehler, G.P., Rudel, R.A., 2007. Environmental pollutants and breast cancer: epidemiologic studies. Cancer Interdiscip. Int. J. Am. Cancer Soc. 109, 2667–2711.
Bulka, C.M., Jones, R.M., Turyk, M.E., Stayner, L.T., Argos, M., 2016. Arsenic in drinking water and prostate cancer in Illinois counties: an ecologic study. Environ. Res. 148, 450–456.
Buonanno, G., Giovinco, G., Morawska, L., Stabile, L., 2015. Lung cancer risk of airborne particles for italian population. Environ. Res. 142, 443–451.
Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., Needham, L.L., 2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. EHP. 116 (1), 39–44.
Cao, Y., Giovannucci, E.L., 2016. Alcohol as a risk factor for cancer. Seminars in Oncology Nursing. Vol. 32, No. 3. WB Saunders, pp. 325–331.
Cazzolla Gatti, R., 2021. Why we will continue to lose our battle with cancers if we do not stop their triggers from environmental pollution. IJERPH 18 (11), 6107.
Cazzolla Gatti, R., Velichevskaya, A., Tateo, A., Amoroso, N., Monaco, A., 2020. Machine learning reveals that prolonged exposure to air pollution is associated with SARS-CoV-2 mortality and infectivity in Italy. Environ. Pollut. 267, 115471.
Chen, X., Zhang, L.W., Huang, J.J., Song, F.J., Zhang, L.P., Qian, Z.M., Trevathan, E., et al., 2016. Long-term exposure to urban air pollution and lung cancer mortality: a 12-year cohort study in northern China. Sci. Total Environ. 571, 855–861.
Clapp, R.W., Jacobs, M.M., Loechler, E.L., 2008. Environmental and occupational causes of cancer: new evidence 2005–2007. Rev. Environ. Health 23, 1–36.
Cohen, A.J., 2000. Outdoor air pollution and lung cancer. EHP 108, 743–750.
Cole, P., Hoover, R., Friedell, G.H., 1972. Occupation and cancer of the lower urinary tract. Cancer 29, 1250–1260.
Cooper, R.L., Stoker, T.E., Tyrey, L., Goldman, J.M., McElroy, W.K., 2000. Atrazine disrupts the hypothalamic control of pituitary-ovarian function. Toxicol. Sci. 53, 297–307.
Davis, D., 2007. The Secret History of the War on Cancer. Basic Books, New York.
Deng, T., Lyon, C.J., Bergin, S., Caligiuri, M.A., Hsueh, W.A., 2016. Obesity, inflammation, and cancer. Annu. Rev. Pathol. 11, 421–449.
Desdoits-Lethimonier, C., Albert, O., Le Bizec, B., Perdu, E., Zalko, D., Courant, F., Lesné, L., Guillé, F., Dejucq-Rainsford, N., Jégou, B., 2012. Human testis steroidogenesis is inhibited by phthalates. Hum. Reprod. 27 (5), 1451–1459.
Di Lorenzo, G., Federico, P., De Placido, S., Buonerba, C., 2015. Increased risk of bladder cancer in critical areas at high pressure of pollution of the Campania region in Italy: a systematic review. Crit. Rev. Oncol. Hematol. 96, 534–541.
Di Paola, A., Cazzolla Gatti, R., Monaco, A., Velichevskaya, A., Amoroso, N., Bellotti, R., d. A ten-year (2009–2018) database of cancer mortality rates in Italy, Dryad. Dataset https://doi.org/10.5061/dryad.ns1rn8pvg.
Durando, M., Kass, L., Piva, J., Sonnenschein, C., Soto, A.M., Luque, E.H., Muñoz-de-Toro, M., 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. EHP. 115 (1), 80–86.
Epicentro, 2021. https://www.epicentro.iss.it/passi/dati/fumo. (Accessed 15 July 2021).
Falcioni, L., Bua, L., Tibaldi, E., Lauriola, M., De Angelis, L., Gnudi, F., Belpoggi, F., 2018. Report of final results regarding brain and heart tumors in Sprague-dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environ. Res. 165, 496–503.
Fierens, S., Mairesse, H., Hermans, C., Bernard, A., Eppe, G., Focant, J.F., Pauw, E.D., 2003. Dioxin accumulation in residents around incinerators. J. Toxicol. Environ. Health A 66 (14), 1287–1293.
Freeman, L.E.B., Rusiecki, J.A., Hoppin, J.A., Lubin, J.H., Koutros, S., Andreotti, G., Hoar Zahm, S., et al., 2011. Atrazine and cancer incidence among pesticide applicators in the agricultural health study (1994–2007). Environ. Health Perspect. 119, 1253–1259.
García-Pérez, J., Pérez-Abad, N., Lope, V., Castelló, A., et al., 2016. Breast and prostate cancer mortality and industrial pollution. Environ. Pollut. 214, 394–399.
García-Pérez, J., Lope, V., Pérez-Gómez, B., Molina, A.J., et al., 2018. Risk of breast cancer and residential proximity to industrial installations: new findings from a multicase-control study (MCC-Spain). Environ. Pollut. 237, 559–568.
García-Pérez, J., Lope, V., Fernández de Larrea-Baz, N., Molina, A.J., et al., 2021. Risk of gastric cancer in the environs of industrial facilities in the MCC-Spain study. Environ. Pollut. 278, 116854.
Gilliom, R.J., Barbash, J.E., Crawford, C.G., Hamilton, P.A., Martin, J.D., Nakagaki, N., Nowell, L.H., Scott, J.C., Stackelberg, P.E., Thelin, G.P., Wolock, D.M., 2006. The Quality of Our Nation's Waters: Pesticides in the Nation's Streams and Ground Water, 1992-2001. U.S. Geological Survey Circular 1291 (2006).
Goncharov, A., Rej, R., Negoita, S., Schymura, M., Santiago-Rivera, A., Morse, G., 2009. Lower serum testosterone associated with elevated polychlorinated biphenyl concentrations in Native American men. EHP. 117 (9), 1454–1460.
Grosse, Y., Baan, R., Straif, K., Secretan, B., Ghissassi, F.E., Cogliano, V., 2006. Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. Lancet Oncol. 7, 628–629.
Gupta, S., Sharma, R.S., Singh, R., 2022. Non-ionizing radiation as possible carcinogen. Int. J. Environ. Health Res. 32 (4), 916–940.
Hannon, P.R., Flaws, J.A., 2015. The effects of phthalates on the ovary. Front. Endocrinol. 6, 8.
Hashim, D., Boffetta, P., 2014. Occupational and environmental exposures and cancers in developing countries. Ann. Glob. Health 80 (5), 393–411.
Ho, S.M., Tang, W.Y., De Frausto, J.B., Prins, G.S., 2006. Developmental exposure to estradiol and bisphenol a increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res. 66 (11), 5624–5632.
Hystad, P., Villeneuve, P.J., Goldberg, M.S., Crouse, D.L., Johnson, K., 2015. Canadian cancer registries epidemiology research group. Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: a case–control study. Environ. Int. 74, 240–248.
IARC, 2022. https://monographs.iarc.who.int/agents-classified-by-the-iarc/. (Accessed 7 June 2022).
Inoue-Choi, M., Weyer, P.J., Jones, R.R., Booth, B.J., Cantor, K.P., Robien, K., Ward, M.H., 2016. Atrazine in public water supplies and risk of ovarian cancer among postmenopausal women in the Iowa Women's health study. Occup. Environ. Med. 73, 582–587.
Institute of Economic and Social Research of Piedmont, 2021. https://www.sisreg.it/index.php?option=com_content&view=article&id=102&Itemid=75. (Accessed 15 July 2021).
Ihsan, R., Chauhan, P.S., Mishra, A.K., Yadav, D.S., Kaushal, M., Sharma, J.D., Zomawia, E., Verma, Y., Kapur, S., Saxena, S., 2011. Multiple analytical approaches reveal distinct gene-environment interactions in smokers and non smokers in lung cancer. PLoS One 6 (12), e29431.
Istat, Annuario Statistico Italiano, 2019. https://www.istat.it/it/files/2019/12/Asi-2019.pdf. (Accessed 15 July 2021).
Italian Ministry of Health, 2019. Annuario Statistico del Servizio Sanitario Nazionale 2017. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2879_allegato.pdf. (Accessed 15 July 2021).
Jackson, J., 1991. A Users Guide to Principal Components. Wiley, New York.
Jain, A.K., 1988. Dubes RC. Algorithms for Clustering Data. Prentice-Hall, New Jersey.
Jones, R.R., Weyer, P.J., DellaValle, C.T., Inoue-Choi, M., Anderson, K.E., Cantor, K.P., Krasner, S., et al., 2016. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. Environ. Health Perspect. 124, 1751–1758.
Kampa, M., Castanas, E., 2008. Human health effects of air pollution. Environ. Pollut. 151 (2), 362–367.
Khan, N., Afaq, F., Mukhtar, H., 2010. Lifestyle as risk factor for cancer: evidence from human studies. Cancer Lett. 293 (2), 133–143.
Kim, D., Martz, J., Violi, A.A., 2014. Surrogate for emulating the physical and chemical properties of conventional jet fuel. Combust. Flame 161, 1489–1498.
Kim, K.E., Cho, D., Park, H.J., 2016. Air pollution and skin diseases: adverse effects of airborne particulate matter on various skin diseases. Life Sci. 152, 126–134.
Kim, H.B., Shim, J.Y., Park, B., Lee, Y.J., 2018. Long-term exposure to air pollutants and cancer mortality: a meta-analysis of cohort studies. Int. J. Environ. Res. Public Health 15 (11), 2608.
Korsh, J., Shen, A., Aliano, K., Davenport, T., 2015. Polycyclic aromatic hydrocarbons and breast cancer: a review of the literature. Breast Care 10, 316–318.
Koutros, S., Lynch, C.F., Ma, X., Lee, W.J., Hoppin, J.A., Christensen, C.H., Andreotti, G., 2009. Heterocyclic aromatic amine pesticide use and human cancer risk: results from the U.S. Agricultural Health Study. Int. J. Cancer 124, 1206–1212.
Kursa, M.B., Rudnicki, W.R., 2010. Feature selection with the boruta package. J. Stat. Softw. 36, 1–13.
Liu, C.C., Chen, C.C., Wu, T.N., Yang, C.Y., 2008. Association of brain cancer with residential exposure to petrochemical air pollution in Taiwan. J. Toxicol. Environ. Health A 71 (5), 310–314.
Liu, C.C., Tsai, S.S., Chiu, H.F., Wu, T.N., Chen, C.C., Yang, C.Y., 2009. Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan. Inhal. Toxicol. 21, 48–54.
Monson, R.R., Nakano, K., 1976. Mortality among rubber workers: I. White male union employees in Akron, Ohio. AJE 103, 284–296.
National Institute of Health, 2021. https://www.epicentro.iss.it/passi/dati/sovrappeso. (Accessed 15 July 2021).
NIOSH, 1980. Special Occupational Hazard Review for Benzidene-Based Dyes, DHEW (NIOSH) Pub. 80–109. NIOSH, Cincinnati, OH, USA.
O'Leary, L.M., Hicks, A.M., Peters, J.M., London, S., 1991. Parental exposures and risk of childhood cancer: a review. Am. J. Ind. Med. 20, 17–35.
Osório-Costa, F., Rocha, G.Z., Dias, M.M., Carvalheira, J.B., 2009. Epidemiological and molecular mechanisms aspects linking obesity and cancer. Arq. Bras. Endocrinol. Metabol. 53 (2), 219–226.
Pan, B.J., Hong, Y.J., Chang, G.C., Wang, M.T., Cinkotai, F.F., Ko, Y.C., 1994. Excess cancer mortality among children and adolescents in residential districts polluted by petrochemical manufacturing plants in Taiwan. JTEH 43, 117–129.
Poulsen, A.H., Hvidtfeldt, U.A., Sørensen, M., Puett, R., Ketzel, M., Brandt, J., et al., 2020. Components of particulate matter air-pollution and brain tumors. Environ. Int. 144, 106046.
Quirós-Alcalá, L., Bradman, A., Nishioka, M., Harnly, M.E., Hubbard, A., McKone, T.E., Ferber, J., Eskenazi, B., 2011. Pesticides in house dust from urban and farmworker households in California: an observational measurement study. Environ. Health 10 (1), 1–15.
Reaves, D.K., Ginsburg, E., Bang, J.J., Fleming, J.M., 2015. Persistent organic pollutants and obesity: are they potential mechanisms for breast cancer promotion? Endocr. Relat. Cancer 22 (2), R69–R86.
Rocco, G., 2016. Survival after surgical treatment of lung cancer arising in the population exposed to illegal dumping of toxic waste in the land of fires ('Terra dei Fuochi') of southern Italy. Anticancer Res. 36, 2119–2124.
Rodgers, K.M., Udesky, J.O., Rudel, R.A., Brody, J.G., 2018. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ. Res. 160, 152–182.
Roh, T., Lynch, C.F., Weyer, P., Wang, K., Kelly, K.M., Ludewig, G., 2017. Low-level arsenic exposure from drinking water is associated with prostate cancer in Iowa. Environ. Res. 159, 338–343.
Rudel, R.A., Attfield, K.R., Schifano, J.N., Brody, J.G., 2007. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer. 109, 2635–2666.

Sakhvidi, M.J.Z., Lequy, E., Goldberg, M., Jacquemin, B., 2020. Air pollution exposure and bladder, kidney and urinary tract cancer risk: a systematic review. Environ. Pollut. 267, 1–13 115328.

Satta, G., Mascia, N., Serra, T., Salis, A., Saba, L., Sanna, S., Cocco, P., 2018. Estimates of environmental exposure to radiofrequency electromagnetic fields and risk of lymphoma subtypes. Radiat. Res. 189 (5), 541–547.

Saxon, A., Diaz-Sanchez, D., 2005. Air pollution and allergy: you are what you breathe. Nat. Immunol. 6 (3), 223–226.

Seachrist, D.D., Bonk, K.W., Ho, S.M., Prins, G.S., Soto, A.M., Keri, R.A., 2016. A review of the carcinogenic potential of bisphenol A. Reprod. Toxicol. 59, 167–182.

Snedeker, S., 2007. Environmental estrogens: effects on puberty and cancer risk. The Ribbon 12, 5–7.

Sjödin, A., Wong, L.Y., Jones, R.S., Park, A., Zhang, Y., Hodge, C., Dipietro, E., McClure, C., Turner, W., Needham, L.L., Patterson Jr., D.G., 2008. Serum concentrations of polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyl (PBB) in the United States population: 2003-2004. Environ. Sci. Technol. 42 (4), 1377–1384.

Sosa, V., Moliné, T., Somoza, R., Paciucci, R., Kondoh, H., Lleonart, M.E., 2013. Oxidative stress and cancer: an overview. Ageing Res. Rev. 12 (1), 376–390.

Straub, C.L., Maul, J.D., Halbrook, R.S., Spears, B., Lydy, M.J., 2007. Trophic transfer of polychlorinated biphenyls in great blue heron (*Ardea herodias*) at Crab Orchard National Wildlife Refuge, Illinois, United States. Arch. Environ. Contam. Toxicol. 52 (4), 572–579.

Steenland, K., Winquist, A., 2020. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ. Res. 110690.

The World's Worst Polluted Places: The Top Ten (of the Dirty Thirty) (New York: Blacksmith Institute).

Thun, M.J., Henley, S.J., Burns, D., Jemal, A., Shanks, T.G., Calle, E.E., 2006. Lung cancer deaths in lifelong non-smokers. JNCI. 98 (10), 691–699.

Tomasetti, C., Li, L., Vogelstein, B., 2017. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science 355 (6331), 1330–1334.

Trichopoulos, D., Petridou, F., 1994. Epidemiologic studies and cancer etiology in humans. Med. Exerc. Nutr. Health. 3, 206–225.

Tritscher, A.M., Goldstein, J.A., Portier, C.J., McCoy, Z., Clark, G.C., Lucier, G.W., 1992. Dose-response relationships for chronic exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in a rat tumor promotion model: quantification and immunolocalization of CYP1A1 and CYP1A2 in the liver. Cancer Res. 52, 3436–3442.

Tsai, S.S., Tiao, M.M., Kuo, H.W., Wu, T.N., Yang, C.Y., 2009. Association of bladder cancer with residential exposure to petrochemical air pollutant emissions in Taiwan. J. Toxicol. Environ. Health A 72, 53–59.

Tsugawa, H., Suzuki, H., 2021. Oxidative stress in stomach cancer. Cancer. Academic Press, pp. 49–54.

Untersmayr, E., Jensen-Jarolim, E., 2008. The role of protein digestibility and antacids on food allergy outcomes. J. Allergy Clin. Immunol. 121 (6), 1301–1308.

Vineis, P., Di Prima, S., 1983. Cutting oils and bladder cancer. Scand. J. Work Environ. Health 9, 449–450.

Vineis, P., Husgafvel-Pursiainen, K., 2005. Air pollution and cancer: biomarker studies in human populations. Carcinogenesis 26, 1846–1855.

Vinson, F., Merhi, M., Baldi, I., Raynal, H., Gamet-Payrastre, L., 2011. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. Occup. Environ. Med. 68 (9), 694–702.

Wang, K., Ma, W., Wu, K., Ogino, S., Chan, A.T., Giovannucci, E.L., Song, M., 2021. Healthy lifestyle, endoscopic screening, and colorectal cancer incidence and mortality in the United States: a nationwide cohort study. PLoS Med. 18 (2), e1003522.

Ward, M.H., Cantor, K.P., Riley, D., Merkle, S., Lynch, C.F., 2003. Nitrate in public water supplies and risk of bladder cancer. Epidemiology 14, 183–190.

White, A.J., Bradshaw, P.T., Hamra, G.B., 2018. Air pollution and breast cancer: a review. Curr. Epidemiol. Rep. 5, 92–100.

Wild, C.P., Weiderpass, E., Stewart, B.W. (Eds.), 2020. World Cancer Report. IARC.

Wilson, N.K., Chuang, J.C., Morgan, M.K., Lordo, R.A., Sheldon, L.S., 2007. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol a, and nonylphenol at home and day-care. Environ. Res. 103 (1), 9–20.

Yeh, H.L., Hsu, S.W., Chang, Y.C., Chan, T.C., Tsou, H.C., Chang, Y.C., Chiang, P.H., 2017. Spatial analysis of ambient PM2. 5 exposure and bladder cancer mortality in Taiwan. Int. J. Environ. Res. Public Health 14, 508.

Young, H.A., Mills, P.K., Riordan, D.G., Cress, R.D., 2005. Triazine herbicides and epithelial ovarian cancer risk in Central California. J. Occup. Environ. Med. 47, 1148–1156.

Zhitkovich, A., 2011. Chromium in drinking water: sources, metabolism, and cancer risks. Chem. Res. Toxicol. 24, 1617–1629.