Several Site-specific Cancers are Increased in the Volcanic Area in Sicily

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Abstract. *Background: Worldwide, thyroid cancer incidence is increased in many volcanic areas. Whether the incidence of other types of cancers are also increased is not known. Materials and Methods: We analyzed cancer registries covering 82% of the population of Sicily to compare the incidence of 34 site-specific types of cancer in area around the volcano Mt. Etna (where thyroid cancer is very high) with adjacent non-volcanic areas. Differences in crude incidence rate ratios (IRR) between the two areas were calculated. Results: Considering 72,197 incident cases, thyroid cancer (IRR=1.68 in females and 1.40 in males) and lymphatic leukemia (IRR: females=1.48, males=1.39) were significantly increased in the volcanic area in both men and women. Hodgkin's lymphoma, stomach and breast cancer in women and prostate cancer in men were also significantly increased in the volcanic area. Conclusion: Several, but not all types of cancers are significantly increased in the volcanic area of Sicily, indicating that an active volcanic environment may be a risk factor for cancer other than thyroid cancer.*

We previously reported a marked increase of thyroid cancer incidence in the volcanic area of Mt. Etna (Catania province) compared to the rest of Sicily (1). An elevated incidence of thyroid cancer had been already reported in other volcanic areas (2-4) but has been never compared to adjacent 'control' areas. Considering the similarity of genetic background and lifestyle in the studied areas, the cause of increased thyroid cancer risk among residents of the volcanic area of Catania might be attributed to environmental factors. This implies the possibility that unrecognized carcinogens from the surrounding volcanic environment may specifically act on thyroid cells, favoring mutagenesis.

One major question of both scientific and public health relevance is whether the association between a volcanic environment and cancer is limited to the thyroid, or also involves other tissues. Tissue-specific mechanisms, in fact, can make different tissues either more susceptible or resistant to the toxic or mutagenic effects of different substances.

The environment of active volcanos is characterized by the presence of increased levels of several chemicals of volcanic origin that may pollute the local atmosphere, water, soil and food chain.

Mt. Etna is the largest volcano in Europe (3.3 km high; base 40×60 km) and is a continuously active basaltic stratovolcano that is persistently degassing, emitting a large mass of volatiles. In addition to CO_2, its plume is rich with SO2, HCl and HF (5) and contains solid particles in different proportions during different periods, according to episodes of strombolian activity. In addition to magmatic degassing, Mt. Etna contains a large aquifer providing drinking and irrigation water to most of the Catania province. In the water of this aquifer, the concentrations of boron, iron, manganese, vanadium and radon (^{222}Ra) are often higher than the maximum admissible concentration (1). In addition, other chemicals are also found at above average concentration in this volcanic area (6). Occasional reports indicate that the volcanic environment may negatively influence the health of residents and is associated with a variety of diseases (7, 8) including cancer (9, 10). However, possible volcano-derived

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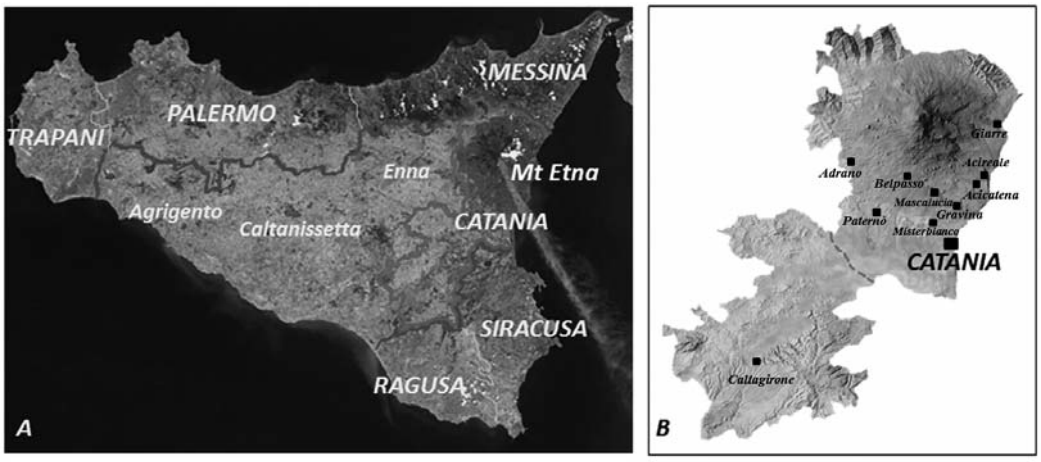

Figure 1. *A: Map of Sicily. The blue line delimits the control area (provinces of Messina, Palermo, Ragusa, Siracusa and Trapani). The red line delimits the volcanic area (Catania province) with Mount Etna indicated. Modified from http://xoomer.virgilio.it/catania.undernet/sicilia%20da%20satellite.jpg. B: Map of the Catania province. The dotted line separates the two major zones of the province (north-eastern area, where Mount Etna is located, and south-western area). Only municipalities with more than 25,000 inhabitants are indicated. Modified from http://static.maphill.com/12/img/t.gif.*

carcinogens, their vehicle for biocontamination and their mechanism of action are unknown.

Being an island, Sicily has well-defined limits and has a large population (5,042,992 inhabitants, ISTAT 2010) (11) with similar genetic background, lifestyles and access to the public health system. The National Healthcare System has been active for decades and is managed at the local level with regional coordination that covers medical assistance for the entire population. Recently, the Regional Epidemiological Observatory (OER) published data from five cancer registries of Sicily providing information on cancer incidence in a large population sample. Therefore, Sicily is a good model to compare cancer incidence in residents of a volcanic area to those in adjacent non-volcanic (control) areas.

Materials and Methods

Patients and areas studied. Population-based cancer registries based on Hospital Discharge Form (SDO) classification and pathology were initiated in Sicily in the early 2000s. These registries vary in size and years of activity; routine indicators of data completeness and quality are satisfactory (12) and internationally recognized (13). Only data covering at least three years from 2003-2007 were used in the present study. All malignant cancer cases (coded according to the 10th International Classification of Diseases, ICD-10 (14), and excluding non-melanoma skin tumors) that were diagnosed in Sicily in the areas covered by these cancer registries (82.2% of the Sicilian population) were extracted from the data published by the Sicily OER in 2013. These data can be accessed from the OER publication web site (http://pti.regione.sicilia.it/portal/page/portal/PIR_PORTALE/PIR_LaStrutturaRegionale/PIR_AssessoratoSalute/PIR_AreeTematiche/PIR_Atlanteoncologico).

Five provinces, Siracusa and Ragusa (2002-2007), Trapani (2002-2006), Palermo (2003-2006) and Messina (2003-2005) for a total population of 3,327,708 inhabitants were considered as control non-volcanic areas (Figure 1A). These control areas include the metropolitan cities of Palermo and Messina.

Combined data from these reference areas were compared against those recorded in the province of Catania (2003-2005), with 1,087,682 residents and characterized by the presence of Mt. Etna. The geology of Catania province is not homogeneous and includes two major zones (Figure 1B): a) the north-eastern area, where the volcano is located, which consists of seven health districts of the Catania province National Health System and hosts the large majority of the population (over 85% of the province inhabitants, including the Catania metropolitan area); b) the south-western part, extending up to 70 km from the top volcano craters, which is more rural and consists of two health districts.

The control non-volcanic areas in Sicily and the Catania province have a similar rural/urban ratio, similar socioeconomic level and public health per-capita expenditure.

No appreciable difference in the age structure was present in the two studied populations, although the age distribution was slightly shifted towards younger ages in the province of Catania. The percentage of the population younger than 50 years was 69.3% vs. 67.1% for males and 65.3% vs. 62.7% for females in the volcanic and the control areas, respectively.

Statistical analysis. Available data on incidence rates (IR) were not age-standardized. Crude cancer incidence in the large control area was set as a reference to allow for calculation of the incidence rate ratio (IRR) between volcanic and non-volcanic areas. Significant excess of cancer incidence in the volcanic area was evaluated on the

Table I. *Cancer incidence in males in the volcanic (Catania province) and non-volcanic areas of Sicily. Cancer types are listed according to the incidence rate ratio (IRR). Significant differences (q-value) are indicated in bold.*

	Volcanic area Inhabitants=524,956 Person-years=1,544,572			Non-volcanic area Inhabitants=1,477,510 Person-years=6,444,871					
Cancer type	Cases/year (n)	IR	95% CI	Cases/year (n)	IR	95% CI	IRR	*p*	*q*
Lymphatic leukemia	164	10.62	10.60-10.63	488	7.57	7.57-7.58	140.23	<0.001	0.002
Thyroid	131	8.48	8.47-8.49	393	6.10	6.09-6.10	139.09	<0.001	0.006
Kaposi sarcoma	30	1.94	1.94-1.95	91	1.41	1.41-1.41	137.56	0.037	0.567
Hodgkin lymphoma	66	4.27	4.27-4.28	206	3.20	3.19-3.20	133.69	0.010	0.243
Gallbladder and biliary tract	129	8.35	8.34-8.37	442	6.86	6.85-6.86	121.78	0.013	0.269
Testis	97	6.28	6.27-6.29	343	5.32	5.32-5.33	118.00	0.049	0.677
Stomach	332	21.49	21.46-21.53	1200	18.62	18.61-18.63	115.44	0.005	0.148
Prostate	1364	88.31	88.17-88.45	5144	79.82	79.75-79.88	110.64	<0.001	0.006
Non-Hodgkin lymphoma	266	17.22	17.19-17.25	1007	15.62	15.61-15.64	110.22	0.054	0.680
Kidney and urinary tract	232	15.02	15.00-15.04	910	14.12	14.11-14.13	106.38	0.164	1.000
Bone	16	1.04	1.03-1.04	63	0.98	0.98-0.98	105.97	0.345	1.000
Colon	661	42.80	42.73-42.86	2610	40.50	40.47-40.53	105.67	0.076	0.863
Bladder	1063	68.82	68.71-68.93	4429	68.72	68.67-68.77	100.15	0.473	1.000
Rectum	317	20.52	20.49-20.56	1392	21.60	21.58-21.62	95.02	0.811	1.000
Lung	1146	74.20	74.08-74.31	5076	78.76	78.70-78.82	94.20	0.978	1.000
Larynx	168	10.88	10.86-10.89	753	11.68	11.67-11.69	93.09	0.813	1.000
Small intestine	19	1.23	1.23-1.23	86	1.33	1.33-1.34	92.19	0.583	1.000
CNS	133	8.61	8.60-8.62	613	9.51	9.50-9.52	90.53	0.866	1.000
Myeloma	94	6.09	6.08-6.10	442	6.86	6.85-6.86	88.74	0.868	1.000
Myeloid leukemia	84	5.44	5.43-5.45	407	6.32	6.32-6.32	86.12	0.909	1.000
Pancreas	172	11.14	11.12-11.15	850	13.19	13.18-13.20	84.43	0.987	1.000
Skin (non melanoma)	1357	87.86	87.72-87.99	6861	106.46	106.37-106.54	82.53	1.000	1.000
Liver	254	16.44	16.42-16.47	1408	21.85	21.83-21.86	75.27	1.000	1.000
Breast	16	1.04	1.03-1.04	90	1.40	1.40-1.40	74.18	0.865	1.000
Soft tissues	33	2.14	2.13-2.14	194	3.01	3.01-3.01	70.98	0.976	1.000
Melanoma	94	6.09	6.08-6.10	556	8.63	8.62-8.63	70.54	1.000	1.000
Oesophagus	26	1.68	1.68-1.69	173	2.68	2.68-2.69	62.71	0.993	1.000
Leukemia (not specified)	15	0.97	0.97-0.97	105	1.63	1.63-1.63	59.61	0.979	1.000
Mesothelioma	21	1.36	1.36-1.36	168	2.61	2.60-2.61	52.16	0.999	1.000
Other sites	221	14.31	14.29-14.33	886	13.75	13.74-13.76	104.08	0.262	1.000
All sites[a]	7718	499.69	498.9-500.5	31499	488.75	488.4-489.1	102.24	0.026	0.461

Corrected overall critical *p*-value=0.0012. IR: Crude incidence rate per 10^5 inhabitants per year; 95% CI: confidence interval; IRR: incidence rate ratio; [a]excluding non-melanoma skin tumors.

basis of the Poisson distribution (*p*-value) adjusted by multiple non-independent comparison tests (one-sided *q*-value). When simultaneously testing a family of hypotheses, controlling the increased type I error is a central issue for multiple comparisons (15). The false-discovery rate (FDR) was calculated as the expected proportion of erroneous rejections among all rejections in order to reduce the false-positive rate among cancer incidence differences to 5% or less, according to the *q*-value. After Yekutieli correction for multiple testing, the corrected overall critical *p*-value was 0.0012 for males (Table I) and 0.0021 for females (Table II). All analyses were performed using commercially available software (Stata version 13; StataCorp, College Station, TX, USA).

Results

The overall comparative analysis between the volcanic and control areas in Sicily, with 32,980 incident cancer cases in females and 39,217 in males, indicated an excess of cancer incidence in the volcanic area that, in terms of IRR, was significantly higher in women (IRR=1.06, *q*=value 0.0001) but not in men (IRR=1.02, *q*-value=0.46).

The increased cancer incidence in the province of Catania was more marked in the seven public health districts of the

Table II. *Cancer incidence in females in the volcanic (Catania province) and non-volcanic areas of Sicily. Cancer types are listed according to the incidence rate ratio (IRR). Significant differences (q-value) are indicated in bold.*

	Volcanic area Inhabitants=562,726 Person-years=1,652,780			Non-volcanic area Inhabitants=1,578,146 Person-years=6,852,290					
Cancer type	Cases/year (n)	IR	95% CI	Cases/year (n)	IR	95% CI	IRR	*p*	*q*
Thyroid	597	36.12	36.07-36.18	1476	21.54	21.52-21.56	167.69	<0.001	<0.001
Lymphatic leukemia	109	6.59	6.58-6.61	305	4.45	4.45-4.45	148.17	<0.001	0.002
Hodgkin lymphoma	62	3.75	3.75-3.76	176	2.57	2.57-2.57	146.05	0.002	0.044
Kaposi sarcoma	14	0.85	0.85-0.85	43	0.63	0.63-0.63	134.98	0.104	1.000
Stomach	234	14.16	14.14-14.18	789	11.51	11.51-11.52	122.96	0.001	0.027
Mesothelioma	14	0.85	0.85-0.85	48	0.70	0.70-0.70	120.92	0.191	1.000
Breast	1960	118.59	118.41-118.77	7312	106.71	106.63-106.79	111.13	<0.001	<0.001
Lung	281	17.00	16.98-17.03	1058	15.44	15.43-15.45	110.11	0.052	0.902
Kidney and urinary tract	119	7.20	7.19-7.21	477	6.96	6.96-6.97	103.43	0.335	1.000
Corpus uteri	383	23.17	23.14-23.21	1543	22.52	22.50-22.53	102.91	0.277	1.000
Rectum	259	15.67	15.65-15.69	1048	15.29	15.28-15.31	102.46	0.333	1.000
Colon	588	35.58	35.52-35.63	2448	35.73	35.70-35.75	99.58	0.529	1.000
Skin (non melanoma)	918	55.54	55.46-55.63	3864	56.39	56.35-56.43	98.50	0.669	1.000
Bladder	185	11.19	11.18-11.21	790	11.53	11.52-11.54	97.09	0.639	1.000
Soft tissues	32	1.94	1.93-1.94	138	2.01	2.01-2.02	96.14	0.543	1.000
Genitals (not specified)	72	4.36	4.35-4.36	311	4.54	4.54-4.54	95.98	0.607	1.000
Pancreas	205	12.40	12.38-12.42	888	12.96	12.95-12.97	95.71	0.721	1.000
Non-Hodgkin lymphoma	189	11.44	11.42-11.45	839	12.24	12.23-12.25	93.39	0.817	1.000
Gallbladder and biliary tract	139	8.41	8.40-8.42	624	9.11	9.10-9.11	92.35	0.815	1.000
Myeloid leukemia	72	4.36	4.35-4.36	325	4.74	4.74-4.75	91.85	0.744	1.000
Myeloma	89	5.38	5.38-5.39	403	5.88	5.88-5.89	91.56	0.781	1.000
Ovary	209	12.65	12.63-12.66	974	14.21	14.20-14.22	88.96	0.953	1.000
Oesophagus	14	0.85	0.85-0.85	69	1.01	1.01-1.01	84.12	0.690	1.000
CNS	91	5.51	5.5-5.51	459	6.70	6.69-6.70	82.20	0.969	1.000
Uterus (not specified)	20	1.21	1.21-1.21	101	1.47	1.47-1.48	82.10	0.779	1.000
Melanoma	101	6.11	6.10-6.12	511	7.46	7.45-7.46	81.94	0.978	1.000
Bone	11	0.67	0.66-0.67	57	0.83	0.83-0.83	80.01	0.718	1.000
Larynx	13	0.79	0.79-0.79	68	0.99	0.99-0.99	79.26	0.757	1.000
Small intestine	13	0.79	0.79-0.79	71	1.04	1.04-1.04	75.91	0.807	1.000
Cervix uteri	93	5.63	5.62-5.64	533	7.78	7.77-7.78	72.34	0.999	1.000
Liver	129	7.81	7.79-7.82	742	10.83	10.82-10.84	72.08	1.000	1.000
Leukemia (not specified)	15	0.91	0.91-0.91	99	1.44	1.44-1.45	62.82	0.964	1.000
Other sites	217	13.13	13.11-13.15	804	11.73	11.72-11.74	111.90	0.047	0.902
All sites[a]	6722	406.71	406.1-407.3	26258	383.20	382.9-383.5	106.13	<0.001	<0.001

Corrected overall critical *p*-value=0.0021. IR: Crude incidence rate per 10^5 inhabitants per year; 95% CI: confidence interval; IRR: incidence rate ratio; [a]excluding non-melanoma skin tumors.

north-eastern part of the province. In this volcanic area, the overall tumor incidence (12,546 cases out of 2,760,051 year/person) was significantly higher than in the two south-eastern health districts (1,894 cases out of 437,301 year/persons; IRR=1.05, *q*-value=0.0048).

Considering the entire Catania province, the higher cancer incidence was primarily due to the statistically significant increase of thyroid cancer (IRR=1.68 and 1.39 in women and men, respectively) and lymphatic leukemia (1.48 and 1.40 in women and men, respectively) (Tables I and II).

Additionally, Hodgkin's lymphoma (IRR=1.46), stomach cancer (IRR=1.23) and breast cancer (IRR=1.11) incidences were significantly increased in women living in the volcanic area (Table II), whereas this level of significance was only achieved for prostate cancer in men (IRR=1.11) (Table I). Hodgkin's lymphoma, Kaposi sarcoma and cancer of testis, stomach, gallbladder and biliary tract were also increased in male residents of the volcanic area but the difference from those in the control area did not reach statistical significance (Tables I and II).

In the Catania province, the incidence of Kaposi sarcoma was increased in both genders (IRR=1.35 in females and 1.38 in males) but because of the paucity of the incident cases recorded (overall 178 cases/year), the difference between the volcanic and control areas did not reach statistical significance.

Discussion

Over 500 million people worldwide live in a volcanic environment. This environment is heterogeneous depending on the type of volcano (shield, composite, *etc*.) and the volcanic activity. Specifically, the frequency and type of volcanic emissions in terms of both degassing and particulate plumes that can deposit in the soil differ between different volcanic environments. Moreover, it is not always water from the volcanic aquifer that is used for both drinking and irrigation, which can influence the environment, the food chain and human biocontamination.

In residents of the volcanic area of Mt. Etna, the incidence of several types of cancers is increased compared to a reference population living in adjacent, non-volcanic areas of the same island (Table I and II). Because the Sicilian population is genetically homogeneous and residence exchange has been well documented over many centuries (16), the differences in cancer incidence might be attributed to either socioeconomic or environmental factors. Lifestyle, access to healthcare, socio-economic status and urban/rural distribution are very similar in the two studied populations. The available data on anthropogenic pollution do not suggest a significant difference between the studied areas, although two industrially polluted sites (Priolo-Melilli-Augusta in the Siracusa province and Milazzo in the Messina province, with nearly 700,000 residents overall) exist in the control areas, while none are present in the volcanic Catania province (17). Moreover, no difference in the prevalence of viral infections, HIV or vaccination has been reported in either of the two populations studied.

Therefore, the only major difference between the studied areas appears to be the volcanic environment that is typical of the Catania province, especially its north-eastern area. The difference in cancer incidence between the strictly volcanic zone of the Catania province close to Mt. Etna and the southwestern area that is far from the volcano further supports the cause–effect relationship between the volcanic environment and increased cancer incidence. Many factors can contribute to the observation that cancer is not increased in the nearby provinces of Messina and Enna, both of which are close to the volcanic craters (Figure 1A). Firstly, the population is unevenly distributed, being highly concentrated in the southeastern side of the volcano and scattered in the northern and western zones. Secondly, the Mt. Etna aquifer, which is a possible vehicle of selective geographic biocontamination, provides drinking water and irrigation to the majority of Catania province, but it provides only minimal water to Messina and does not serve the Enna province. Thirdly, the prevailing winds in the Mt. Etna region area are from the west and north-west (18), carrying fallout and particles present in the gaseous volcanic plume away from the provinces located north and west of Catania. Moreover, the local wind field with downslope surface winds force the gaseous volcanic plume to follow the steep morphology, especially during the night (19). This will cause prevalent atmospheric pollution and dispersion of the finest ash fallout in the volcanic area. Therefore, the relationship between the volcanic environment and increased cancer incidence is highly plausible and further supported by previous observations on increased cancer risk in volcanic areas (9, 10) and by the high frequency of markers of DNA damage in residents of volcanically-active areas (20).

The causes and the mechanisms of the carcinogenic potential of the volcanic environment are unknown. Areas that are close to volcanic activity are characterized by non-anthropogenic pollution that involves the atmosphere, soil and water. As a consequence, the local food chain may also be polluted with a variety of trace elements that may be present in various chemical forms. Increased exposure to these elements in either inorganic or organic forms by inhalation, skin contact and digestion may favor cancer initiation and progression.

Environmental carcinogens can differentially affect cells and tissues depending on how specific tissues are exposed to them and the sensitivity of individual tissues determined by transport, disposition and accumulation of the compound (toxicokinetics and toxicodynamics). In addition, tissue-specific functional organization, including the rate of cell proliferation and the presence of stem and precursor cells, may play a role. These factors may explain why specific cancer types are increased in volcanic areas.

The relationship between thyroid cancer and the volcanic environment is not a new finding since it has already been reported in different volcanic areas in Europe and Pacific islands (1-4). In spite of these previous observations, thyroid cancer incidence has not been investigated in many highly populated volcanic areas such as Japan and Indonesia, where a surveillance effort should be suggested.

An increased risk of hematopoietic and lymphatic tissue cancer in individuals using volcanic geothermal hot water has already been reported (10). However, for these types of cancer, viral or bacterial infections and exposure to ionizing radiation, especially during childhood, have been emphasized as risk factors rather than exposure to inorganic environmental pollutants (21, 22). The cause of increased incidence of lymphatic leukemia and Hodgkin's lymphoma in our study, moreover, may not be the same: different pollutants and different mechanisms may be responsible.

The two major gender-specific cancer types (breast cancer in females and prostate cancer in males) have only slightly increased IRRs (both +11%) relative to the control area, which reach statistical significance because of the large number of cases (Tables I and II). In contrast, other cancer types are clearly increased in the volcanic area compared to the control area, but the statistical strength of the observed difference is low. The incidence of Kaposi sarcoma is remarkably increased in the volcanic province of Catania for both genders (IRR=1.35 in females and 1.38 in males) but due to the limited number of cases, the difference does not reach significance. The association between this tumor and the volcanic environment (23, 24) has already been reported in Sicily (25) and a possible role of iron and alumino-silicate clay has been suggested. However, the mechanism for it is elusive: environmental factors may have a direct carcinogenic effect or may have an indirect effect, by immunocompromising predisposed individuals.

Our study has certain limitations. These may be related to the cancer registry data, the fact that the data do not cover the entire island of Sicily, and the fact that reported incidences are crude values that are not age-standardized. However, the slightly younger average age and the lack of industrial polluted areas in the volcanic province of Catania with respect to the control areas suggest that the differences might be under- rather than overestimated. It must also be highlighted that the possibility of unknown confounders cannot be excluded in this study because volcanic pollutants are not characterized and information on the precise chemical and physical exposure of the population to these pollutants is not available.

The strengths of the study are the large population evaluated and the simultaneous evaluation of the volcanic and adjacent non-volcanic areas that are homogeneous in terms of genetic, lifestyle and socioeconomic characteristics and are both well-delimited and comparable for the Public Health System.

In conclusion, in the volcanic area of Mt. Etna, we found a small increase in total cancer incidence and larger increases for several tissue-specific types of cancer, which is a likely consequence of non-anthropogenic environmental pollution. The increased incidence of different tumor types in residents of the volcanic area suggests that different cancer-specific carcinogens and mechanisms may be responsible. Further studies are warranted to confirm these observations and to investigate the carcinogens involved and the underlying mechanisms leading to tumorigenesis. The identification of these factors could be important for better understanding cancer biology and developing preventative measures.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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