

Papillary Thyroid Cancer Incidence in the Volcanic Area of Sicily

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- Background** The steadily increasing incidence of thyroid cancer has been attributed mostly to more sensitive thyroid nodule screening. However, various environmental factors, such as those associated with volcanic areas, cannot be excluded as risk factors. We evaluated thyroid cancer incidence in Sicily, which has a homogeneous population and a province (Catania) that includes the Mt Etna volcanic area.
- Methods** In a register-based epidemiological survey, we collected all incident thyroid cancers in Sicily from January 1, 2002, through December 31, 2004. The age-standardized incidence rate for the world population (ASR_w) was calculated and expressed as the number of thyroid cancer diagnoses per 100 000 residents per year. The association of thyroid cancer incidence rate with sex, age, tumor histotype, and various environmental factors was evaluated by modeling the variation of the ASR_w . All statistical tests were two-sided.
- Results** In 2002–2004, 1950 incident thyroid cancers were identified in Sicily (among women, $ASR_w = 17.8$, 95% confidence interval [CI] = 16.9 to 18.7; and among men, $ASR_w = 3.7$, 95% CI = 3.3 to 4.1). Although the percentage of thyroid cancers that were microcarcinomas (ie, ≤ 10 mm) and ratio of men to women with thyroid cancer were similar in all nine Sicilian provinces, thyroid cancer incidence was statistically significantly higher in the province of Catania (among women, $ASR_w = 31.7$, 95% CI = 29.1 to 34.3; and among men, $ASR_w = 6.4$, 95% CI = 5.2 to 7.5) than in the rest of Sicily (among women, $ASR_w = 14.1$, 95% CI = 13.2 to 15.0; and among men, $ASR_w = 3.0$, 95% CI = 2.6 to 3.4) (all P values $< .001$). Incidence of papillary, but not follicular or medullary, cancers was statistically significantly increased in Catania province, and papillary tumors from patients in Catania more frequently carried the *BRAF* V600E gene mutation (55 [52%] of 106 tumors) than tumors from patients elsewhere in Sicily (68 [33%] of 205 tumors) (relative risk = 1.7, 95% CI = 1.0 to 2.8, $P = .02$). Cancer incidence was statistically significantly lower in rural areas than in urban areas of Sicily ($P = .003$). No association with mild iodine deficiency or industrial installations was found. Levels of many elements (including boron, iron, manganese, and vanadium) in the drinking water of Catania province often exceeded maximum admissible concentrations, in contrast to water in the rest of Sicily.
- Conclusion** Residents of Catania province with its volcanic region appear to have a higher incidence of papillary thyroid cancer than elsewhere in Sicily.

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The incidence of thyroid cancer is increasing more rapidly than that of other cancers in the United States (1,2), and its incidence is increasing in many other countries, including France (3) and Italy (4). The average incidence of thyroid cancer among women and men is 14.1 and 4.9 diagnoses per 100 000 residents per year, respectively, in the white population of the United States (5) and 12.9 and 5.0 diagnoses per 100 000 residents per year, respectively, in Europe (6). In Italy, the average incidence among women and men is 15.5 and 5.2 diagnoses per 100 000 residents per year, respectively. (4). In the United States, thyroid cancer is currently the eighth most common malignancy among women, accounting for 3% of all cancers, compared with 1.7% (and ranking 14th) 20 years ago, with an annual increase of 1.4% since 1990 (7). Many experts attribute this increasing incidence to more intensive and sensitive

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CONTEXT AND CAVEATS

Prior knowledge

Although increased incidence of thyroid cancer worldwide has been attributed to more sensitive screening, environmental factors, including those associated with volcanic areas, have not been excluded as risk factors.

Study design

Data on all incident thyroid cancers in Sicily were collected from 2002 through 2004. The association of thyroid cancer incidence rate with sex, age, tumor histotype, and various environmental factors was evaluated.

Contribution

Thyroid cancer incidence was statistically significantly higher in the province of Catania, which contains the Mt Etna volcanic area, than in the rest of Sicily. Incidence of papillary, but not follicular or medullary, cancers was statistically significantly increased in Catania province, and papillary tumors from patients in Catania more frequently carried the *BRAF* V600E gene mutation that has been associated with thyroid cancer.

Implications

Residents of the volcanic environment of Mt Etna appear to be at increased risk of papillary thyroid cancer. Investigations to identify specific risk factors for thyroid cancer in this and other volcanic environments are warranted.

Limitations

The population of Sicily is fairly homogenous and so results may not be generalizable to other populations. It was assumed, without evidence, that the composition and concentrations of volcanic contaminants were similar over time. No dose–response associations were identified. Individual-level exposure data to volcanic contaminants were not available.

From the Editors

diagnostic procedures to detect thyroid nodules and to diagnose microcarcinomas (1,8). If these procedures were the only reasons for the increased incidence, we would expect mortality from thyroid cancer to be decreasing because of earlier diagnosis and better management (eg, see <http://seer.cancer.gov/statfacts/html/prost.html>). However, thyroid cancer mortality has remained unchanged (1,6) or even increased in recent years (5,7,9). Moreover, incidence rates of thyroid cancer from 1998 through 2005 increased in the United States for all tumor sizes in both men and women (10). Therefore, a true increase in incidence, in addition to an artificial increase that can be attributed to better screening and diagnosis, is a likely possibility.

Environmental carcinogens associated with an industrialized lifestyle might contribute to the increasing thyroid cancer incidence. Until now, however, the only environmental factors that have been strongly associated with thyroid cancer are exposure to radiation (11) and iodine deficiency (12). An increased incidence of thyroid cancer has also been reported in volcanic areas (13–17) with basaltic characteristics, such as the volcanic regions of Iceland (14) and Hawaii (17). The Mt Etna volcano in Sicily also has basaltic characteristics and hosts a major aquifer that provides

drinking water to more than 750 000 inhabitants and irrigation to large agricultural areas nearby. Water from this aquifer and the volcanic soil undergo a magmatic-type interaction, in which excess CO₂ in volcanic gas leads to acidification of water and to leaching of chemicals from the basalt rock, especially on the lower south-southwestern and eastern flanks of the volcano (18). Various elements and chemicals (including HCO₃, SO₄, calcium, fluoride, chloride, magnesium, boron, manganese, iron, and vanadium and their salts and also ²²²radon) are often increased in water samples from various sources of this volcanic aquifer (18–21), as reported in studies of water samples in other volcanic areas (22,23). The Sicily Island has rural and urban areas, industrial and nonindustrial areas, areas of low and adequate iodine intake, volcanic and nonvolcanic areas, and a homogenous population; thus, Sicily is a favorable setting for the evaluation of environmental influences on thyroid cancer etiology. We therefore evaluated thyroid cancer incidence in each province of Sicily and investigated the relationship of the incidence of thyroid cancer to the environmental characteristics to assess whether additional and, perhaps, still unrecognized environmental factors play a role in thyroid carcinogenesis.

Subjects and Methods

Geographic and Environmental Characteristics

Sicily is a 25 707-km² Mediterranean island with a homogenous and stable population of 4 980 352 inhabitants in 2001 according to the Italian Institute for Statistics (<http://dawinci.istat.it/daWinci/jsp/daWinci.jsp?q=pl02000101932001>). The population is distributed in nine provinces, including 390 municipality districts (Figure 1, A). Sicily has an environment with many different characteristics, including volcanic areas, rural and urban areas, and industrial and nonindustrial areas. Briefly, approximately 84% of the inhabitants of Catania province live in the volcanic area of Mt Etna, the largest and most active volcano in Europe. Therefore, in this study, the environment of the entire province of Catania was considered to be volcanic. The other eight provinces of Sicily are nonvolcanic. Nearly 25% of the Sicilian population lives in rural areas (defined as having population density of ≤150 inhabitants per square kilometer) with mainly agricultural activities. Urban areas have high-density population with mainly commercial and tertiary activities. Approximately 8% of the Sicilian population lives in areas characterized by extensive industrial installations, including mainly chemical, mechanical, and refinery plants. Finally, approximately 5% of the Sicilian population lives in areas of mild-to-moderate iodine deficiency, as determined by more than 30 years of continuous studies of endemic goiters, including goiter surveys in schoolchildren and measurements of urinary iodine and radioiodine thyroid uptake in adults (25–27).

Study Subjects

The Sicilian Regional Registry for Thyroid Cancer was instituted in January 2002. Data on patients with thyroid cancer were collected by blinded specialists from the Medical Schools of Catania (eastern and southeastern Sicily), Messina (Messina province), and Palermo (western Sicily) who surveyed each of the 24 pathology centers in Sicily at regular intervals. Data on patients with any

histological diagnoses of thyroid cancer were collected by following the privacy data directive of the European Union (28). The date of surgery was considered as the date of diagnosis.

Clinical data for more than 90% of patients were obtained from surgical records at the time of thyroidectomy. Recruitment accuracy was verified by independent reuptake of data for patients with thyroid cancer, with cross-checking to eliminate prevalent cases of thyroid cancer. National Health Service hospital's discharge form files were provided by the Sicilian Epidemiological Observatory for diagnoses of thyroid cancer according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code 193)*, thyroidectomy (*ICD-9-CM code 064*), and acquired hypothyroidism (*ICD-9-CM code 2440*). Only patients with a histopathologic diagnosis of thyroid cancer according to the *International Classification of Diseases for Oncology* (ie, *ICD-O code C73.9*) were included.

Determination of the cancer histotype was performed according to World Health Organization guidelines (29) by considering the following four histological subgroups: papillary thyroid cancer (including all variants), follicular thyroid cancer (including all variants), undifferentiated or anaplastic thyroid cancer, and medullary thyroid cancer. Histological accuracy was verified by blind review of slides from approximately 100 thyroid cancers by an expert thyroid cancer pathologist. Tumors were staged according to the TNM staging sixth edition (30). Patient age, tumor size, lymph node status, and extra-thyroid invasion were assessed.

Laboratory Methods

Specimens of water, both groundwater and tap water, from the Mt Etna aquifer have been collected and analyzed by the Regional Environmental Protection Agency since 1993. For this study, measurements of boron, iron, manganese, and vanadium (all frequently exceeding the maximum admissible concentration and considered potentially dangerous for human health) were performed in 2006–2007 on specimens from the Mt Etna aquifer and compared with those from the provinces of Palermo and Ragusa. Samples were collected according to the procedure required by the official instructions (code 1030) of the Environmental Protection Agency and the Italian National Research Council (31) and were stored at 4°C. The elements were measured by an atomic emission spectrophotometer (Plasma 400; Perkin-Elmer, Waltham, MA) as the total amount of each element (ie, both in the free state and in salts).

The most frequent genetic alteration in papillary thyroid cancer is the *BRAF* V600E mutation, in which the valine at position 600 is replaced with glutamic acid. We analyzed in 311 randomly selected specimens of classic papillary thyroid cancer from different areas of Sicily (106 from the volcanic area and 205 from nonvolcanic areas) by directly sequencing *BRAF* exon 15 DNA that had been amplified by use of the polymerase chain reaction (PCR) (32).

Briefly, genomic DNA was extracted by use of Pico Pure DNA extraction kit (Arcturus Bioscience, Mountain View, CA) according to the manufacturer's recommendations. The samples were immediately placed into 50 μ L of proteinase K DNA extraction solution and incubated at 65°C for 16 hours. Samples were subsequently heated at 95°C for 10 minutes to inactivate the proteinase K and centrifuged at 12 000g for 3 minutes, and the supernatant



B (modified from (24))

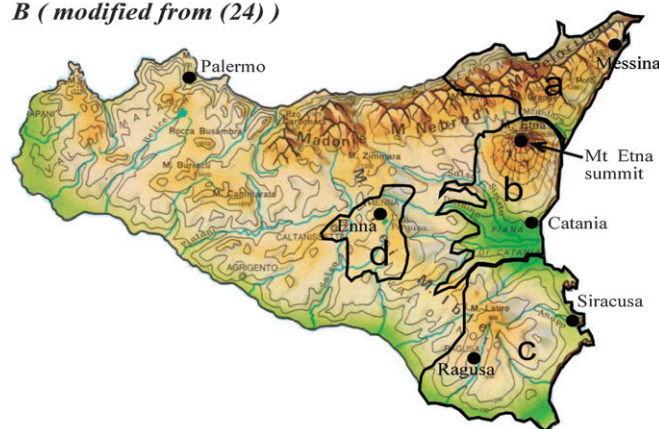


Figure 1. Maps of the island of Sicily. **A**) Thyroid cancer incidence and geography. Borders of the nine provinces are indicated. The province of Catania is lightly shaded. The darkly shaded area indicates the base of Mt Etna edifice. Provinces with the three major cities, Catania, Messina, and Palermo, contain approximately 60% of the Sicilian population. Thyroid cancer incidence values per 100 000 residents per year among women (F) and among men (M) in each province are also indicated. **B**) Main aquifer systems in Eastern Sicily. This map is a modification of a previously published map (24). **a**) Aquifer system of Peloritani Mountains (Messina province). **b**) Aquifer system of Mt Etna and the Catania plain. This system provides drinking water to more than 750 000 inhabitants of the Catania province and irrigation water to a large agricultural area. Areas on the north and west sides of Mt Etna are lightly populated mountain areas. **c**) Aquifer system of Hyblean Uplands (Siracusa and Ragusa province). **d**) Aquifer system of the Erei Mountains (Enna province).

was collected. DNA concentration was measured with a NanoDrop ND-1000 spectrophotometer (Wilmington, DE) and then used as template for PCR amplification and sequencing analysis. The following intron-based PCR primers were designed to amplify the *BRAF* exon 15: forward, TCATAATGCTTGCTCTGATAGGA; and reverse, GGCCAAAATTTAATCAGTGGA. PCRs were performed under the following standard PCR conditions: 95°C for 5 minutes; 40 cycles of 94°C for 30 seconds, 58°C for 30 seconds, and 72°C for 30 seconds; and 70°C for 10 minutes.

Statistical Analysis

Population data (province and town of residence, sex, and age) from the Italian Institute for Statistics were used to estimate the average population for each year studied by linear interpolation.

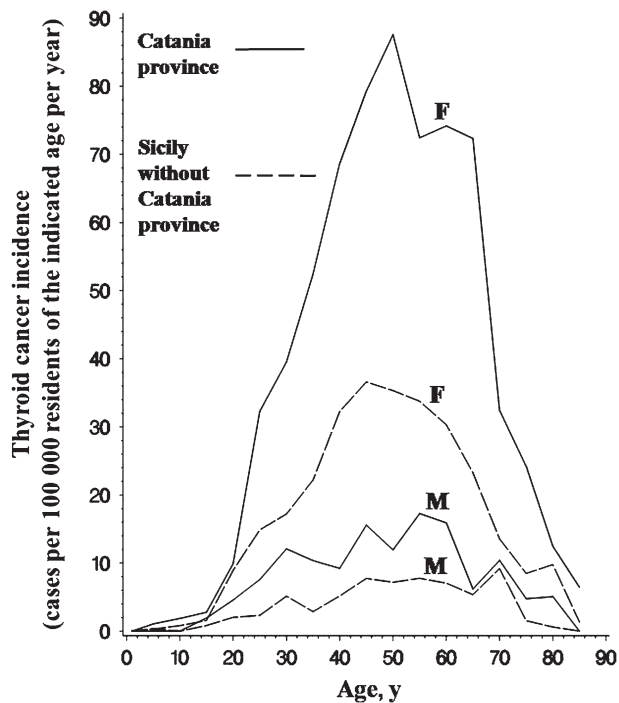


Figure 2. Thyroid cancer incidence in Sicily by sex and age. Age was divided into 5-year groups. M = men; F = women; solid lines = Catania province; dotted lines = rest of Sicily.

Data were expressed as the number of new diagnoses per 100 000 residents per year. Sex- and 5-year age group-specific incidence rates were calculated. Crude and age-standardized incidence rates for the world population (ASR_w) (33) and their 95% confidence intervals (CIs) were calculated by assuming that the observed number of thyroid cancer diagnoses followed a Poisson distribution. Overdispersion relative to Poisson distribution hypothesis was tested by comparing the difference in log likelihood of models obtained when fitting the data by use of the Poisson distribution model and when fitting the negative binomial distribution to a χ^2 distribution with 1 *df*.

Analysis of risk factors was performed by use of Poisson regression models (33) and SAS (version 9.2; SAS Institute, Inc, Cary, NC) and Egret (version 2.0; Cytel Software, Inc, Cambridge, MA) software, and all analyses were adjusted for age and sex, including the number of person-years at risk as an offset variable in each Poisson cell. We considered *P* values that were less than .05 to be statistically significant. All tests of statistical significance were two-sided.

The role of a parameter was tested by subtracting the deviance when fitting models with and without the parameter, and the obtained values were compared by use of the χ^2 distribution with the *df* equal to the number of modalities of the parameter minus one (33). The 95% confidence intervals were estimated by use of the method of maximum likelihood (34).

Results

Thyroid Cancer Incidence in Sicily

In Sicily, 1950 patients were newly diagnosed with thyroid cancer from January 1, 2002, through December 31, 2004 (622 in 2002,

677 in 2003, and 651 in 2004). For this period, the ratio of women to men was 4.3 to 1.0 (ie, 1584 women and 366 men were diagnosed with thyroid cancer from 2002 through 2004). Among both women and men, the age group of 40–60 years had the highest incidence of thyroid cancer (Figure 2), as expected in most populations. The crude annual incidence was 21.9 diagnoses per 100 000 residents per year at risk (95% CI = 20.9 to 23.0) among women with an ASR_w of 17.8 diagnoses per 100 000 residents per year (95% CI = 16.9 to 18.7); among men, crude annual incidence was 4.7 diagnoses per 100 000 residents per year at risk (95% CI = 4.3 to 5.2) with an ASR_w of 3.7 diagnoses per 100 000 residents per year (95% CI = 3.3 to 4.1) (Table 1).

Thyroid Cancer Incidence and Environmental Characteristics

We then evaluated the relationship between thyroid cancer incidence and the different environmental characteristics in the island of Sicily. When we compared incidence rates of thyroid cancer between volcanic and nonvolcanic areas in Sicily, the thyroid cancer incidence rate was very high in the province of Catania volcanic area among women (ASR_w = 31.7 diagnoses per 100 000 residents per year, 95% CI = 29.1 to 34.3) and men (ASR_w = 6.4 diagnoses per 100 000 residents per year, 95% CI = 5.2 to 7.5). These values were statistically significantly higher than those observed in the rest of Sicily among women (ASR_w = 14.1 diagnoses per 100 000 residents per year, 95% CI = 13.2 to 15.0) and men (ASR_w = 3.0 diagnoses per 100 000 residents per year, 95% CI = 2.6 to 3.4, *P* < .001 after adjusting for age and sex) (Table 1 and Figures 1, A and 2). No differences in thyroid cancer incidence were observed in the ratio of women to men between the different provinces.

When we compared incidences of thyroid cancer between rural and urban areas, we found that thyroid cancer incidence was statistically significantly lower in rural areas (among women, ASR_w = 16.4 diagnoses per 100 000 residents per year, 95% CI = 14.6 to 18.2; and among men, ASR_w = 3.3 diagnoses per 100 000 residents per year, 95% CI = 2.5 to 4.3) than in urban areas (among women, ASR_w = 18.2 diagnoses per 100 000 residents per year, 95% CI = 17.2 to 19.2; and among men, ASR_w = 3.9 diagnoses per 100 000 residents per year, 95% CI = 3.4 to 4.3) (*P* = .003 between urban and rural areas, adjusted for age and sex) (Table 1).

When we compared the incidence of thyroid cancer between industrial and nonindustrial areas, we found that fewer residents from industrial areas were diagnosed with thyroid cancer in 2002–2004 (*n* = 119) than those from all other areas of Sicily (*n* = 1831), a borderline statistically significant difference (*P* = .05) (Table 1). However, the difference was no longer apparent after adjustment for the presence of volcanic areas, which contain no industrial area (*P* = .46).

When we compared the incidence of thyroid cancer in areas of low and normal iodine intake, we found that 86 thyroid cancers were diagnosed among 208 512 residents of areas with mild-to-moderate iodine deficiency, scattered over the island, most in the central highlands; this incidence was similar to that of the rest of Sicily (*n* = 1864 among 4 771 840 residents) (*P* = .84) (Table 1). Papillary thyroid cancers accounted for 1664 (89.3%) of all 1864 thyroid cancer diagnoses in iodine-sufficient areas and 75 (87.2%)

Table 1. Thyroid cancer incidence in Sicily: age-standardized rates for the world population (ASR_w) for the entire island and by environmental characteristic*

Environmental characteristic	No. of residents	Women		Men		P†
		No. of thyroid cancers diagnosed	ASR _w (95% CI)	No. of thyroid cancers diagnosed	ASR _w (95% CI)	
Total for all Sicily	4980352	1584	17.8 (16.9 to 18.7)	366	3.7 (3.3 to 4.1)	
Volcanic environment						
Yes (Catania province)	1059811	599	31.7 (29.1 to 34.3)	130	6.4 (5.2 to 7.5)	<.001
No (Sicily without Catania province)	3920541	985	14.1 (13.2 to 15.0)	236	3.0 (2.6 to 3.4)	
Rural	1133529	332	16.4 (14.6 to 18.2)	73	3.3 (2.5 to 4.3)	.003
Urban	3846823	1252	18.2 (17.2 to 19.2)	293	3.9 (3.4 to 4.3)	
Industrial	364110	93	14.1 (11.2 to 17.0)	26	3.8 (2.2 to 5.4)	.05‡
Nonindustrial	4616242	1491	18.1 (17.2 to 19.0)	340	3.7 (3.3 to 4.1)	
Iodine deficiency	208512	68	19.2 (14.4 to 23.8)	18	4.4 (2.2 to 6.6)	.84
Iodine sufficiency	4771840	1516	17.7 (16.8 to 18.4)	348	3.7 (3.3 to 4.1)	

* CI = confidence interval.

† Two-sided test from a Poisson regression analysis, adjusted for sex and age.

‡ When volcanic area (where no industrial zone is present) were excluded, $P = .46$.

of the 86 thyroid cancer diagnoses in iodine-deficient areas. In addition, after adjustment for age and sex, the ratios of papillary thyroid cancers to follicular thyroid cancers remained similar between the two areas that differed by iodine intake ($P = .82$).

When we analyzed all environmental characteristics, a statistically significant ($P < .001$) overdispersion relative to the Poisson distribution was present in all provinces except for that in Catania province. Whatever environmental characteristics were studied, a statistically significant ($P < .001$) overdispersion relative to the Poisson distribution remained, which means that other sources of variability remained uncontrolled. In contrast, when we introduced geographic area (Catania vs the rest of Sicily) into the model, overdispersion disappeared. When we fitted a model that included age, sex, and Catania province, we found no overdispersion (ie, $-2[\log \text{likelihood}\{\text{Poisson}\} - \log \text{likelihood}\{\text{negative binomial}\}] = [-2029.09 - (-2029.09)] = 0$).

Tumor Size, Histotype, and the Prevalence of *BRAF* Mutations

We found that 1126 (57.7%) of all thyroid tumors in Sicily were microcarcinomas (maximum diameter ≤ 10 mm). The distribution of microcarcinomas was similar in all nine provinces in Sicily. Among the 1126 microcarcinomas, 733 (65.1%) were nonaggressive low-risk tumors (ie, unifocal, pT1, N0, M0, and mostly incidental). Also for these low-risk tumors, we found essentially no

difference in the frequency between Catania province (ie, 288 [39.5%] low-risk thyroid tumors among a total of 729 thyroid tumors) and the rest of Sicily (445 [36.5%] low-risk tumors among a total of 1221 tumors) ($P = .19$). When we excluded microcarcinomas and evaluated only thyroid cancers larger than 10 mm in diameter, a statistically significantly higher incidence of larger thyroid cancers was found in the Catania province (among women, ASR_w = 12.3 diagnoses per 100 000 residents per year, 95% CI = 10.7 to 13.9; and among men, ASR_w = 2.5 diagnoses per 100 000 residents per year, 95% CI = 1.8 to 3.2) than in the rest of Sicily (among women, ASR_w = 6.1 diagnoses per 100 000 residents per year, 95% CI = 5.5 to 6.7; and among men, ASR_w = 1.5 diagnoses per 100 000 residents per year, 95% CI = 1.2 to 1.8) (Table 2) (rate ratio for large thyroid cancers between Catania province and the rest of Sicily = 2.0, 95% CI = 1.7 to 2.3, $P = .001$).

When thyroid cancers were analyzed by histotype, papillary thyroid cancer was diagnosed in 1739 (89.2%) of the 1950 patients with thyroid cancer in Sicily. In the Catania province, 686 (94.1%) of the 729 thyroid cancers diagnosed were papillary thyroid cancers. In the rest of Sicily, 1053 (86.2%) of all 1221 tumors diagnosed were papillary thyroid cancers ($P < .001$ with respect to Catania province, after adjusting for age and sex) (Table 3). No statistically significant difference was observed for the other thyroid cancer histotypes between Catania province and the rest of Sicily.

Table 2. Incidence of thyroid microcarcinomas and carcinomas larger than 10 mm in diameter in Sicily*

Area	Sex	Microcarcinomas (≤ 10 mm)		Carcinomas > 10 mm	
		No.	ASR _w (95% CI)	No.	ASR _w (95% CI)
All Sicily	F	931	10.4 (9.7 to 11.1)	653	7.4 (6.8 to 8.0)
	M	195	2.0 (1.7 to 2.3)	171	1.7 (1.5 to 2.0)
Sicily without Catania province	F	564	8.0 (7.3 to 8.7)	421	6.1 (5.5 to 6.7)
	M	118	1.5 (1.2 to 1.8)	118	1.5 (1.2 to 1.8)
Catania province	F	367	19.3 (17.3 to 21.3)	232	12.3 (10.7 to 13.9)
	M	77	3.9 (3.0 to 4.8)	53	2.5 (1.8 to 3.2)

* ASR_w = age-standardized rates for the world population; CI = confidence interval; F = female; M = male.

Table 3. Thyroid cancer incidence in Sicily according to histotypes*

Area	Sex	Histotype																	
		Papillary			Follicular			Undifferentiated and anaplastic			Medullary			Others			Papillary follicular		
		No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	No. of cases	ASR _w (95% CI)	F/M ratio	
All Sicily	F	1431	16.5 (15.3 to 17.0)	110	1.0 (1.2 to 1.4)	13	0.09 (0.04 to 0.15)	26	0.31 (0.19 to 0.43)	4	0.04 (0.00 to 0.08)	4	0.04 (0.00 to 0.08)	4	0.04 (0.00 to 0.08)	4	0.04 (0.00 to 0.08)	13.1	8.6
Sicily without	M	308	3.2 (2.8 to 3.6)	36	0.3 (0.2 to 0.5)	10	0.07 (0.03 to 0.12)	11	0.13 (0.04 to 0.21)	1	0.01 (0.00 to 0.03)	1	0.01 (0.00 to 0.03)	1	0.01 (0.00 to 0.03)	1	0.01 (0.00 to 0.03)	9.8	6.6
Catania province	F	862	12.4 (11.4 to 13.2)	88	1.2 (1.0 to 1.5)	10	0.09 (0.03 to 0.15)	21	0.32 (0.18 to 0.46)	4	0.05 (0.00 to 0.09)	4	0.05 (0.00 to 0.09)	4	0.05 (0.00 to 0.09)	4	0.05 (0.00 to 0.09)	25.9	16.7
Catania province	M	191	2.5 (2.1 to 2.9)	29	0.4 (0.2 to 0.5)	6	0.05 (0.01 to 0.09)	10	0.15 (0.05 to 0.25)	0	0.00	0	0.00	0	0.00	0	0.00	9.8	6.6
Catania province	F	569	30.2 (27.7 to 32.8)	22	1.1 (0.6 to 1.5)	3	0.11 (0.00 to 0.24)	5	0.29 (0.03 to 0.54)	0	0.00	0	0.00	0	0.00	0	0.00	25.9	16.7
Catania province	M	117	5.8 (4.7 to 6.9)	7	0.3 (0.06 to 0.9)	4	0.16 (0.00 to 0.33)	1	0.05 (0.00 to 0.14)	1	0.05 (0.00 to 0.14)	1	0.05 (0.00 to 0.14)	1	0.05 (0.00 to 0.14)	1	0.05 (0.00 to 0.14)	25.9	16.7

* ASR_w = age-standardized rates for the world population; CI = confidence interval; F = female; M = male.

The *BRAF* V600E mutation is the most frequent genetic alteration in papillary thyroid cancer. Because the papillary histotype occurred at increased rate in the volcanic area than in the rest of Sicily, we investigated the prevalence of the *BRAF* V600E mutation in 311 randomly selected classical variant papillary cancers. Among 106 papillary thyroid cancers that were diagnosed in residents from Catania province, 55 (52%) were positive for the *BRAF* V600E mutation. In contrast, among the 205 papillary thyroid cancers that were diagnosed in residents from the rest of Sicily, 68 (33%) were positive for the mutation (relative risk = 1.7, 95% CI = 1.0 to 2.8, *P* = .02, after adjusting for age, sex, and percentage of microcarcinomas).

Chemical Measurements in Water From Three Provinces in Sicily

Drinking water from springs, wells, and tap water in the Mt Etna area, but not in two other provinces of Sicily (Palermo and Ragusa), contained concentrations of boron, iron, manganese, and vanadium that often exceeded their maximum admissible concentrations (Table 4). These elements were also present in water from deep wells and, therefore, most likely are not due to man-made pollution. Concentrations of boron, iron, manganese, and vanadium were different in drinking water samples from the various districts of Catania province possibly because of different groundwater sources and pipeline networks.

Discussion

We found that thyroid cancer incidence was 2.3-fold higher in the volcanic area of Mt Etna in the Sicilian province of Catania than in the other nonvolcanic provinces of Sicily (Figure 1, A). The increased incidence appeared to be associated with an increased incidence of the papillary histotype of thyroid cancer (Table 3).

The increased incidence of thyroid cancer in the volcanic area of Catania province did not appear to be associated with genetic differences in the Sicilian population or to increased or better screening for thyroid nodules and cancer for several reasons. Sicily has a homogeneous and stable population, as assessed by socioeconomic status and by lifestyle. The ratio of women to men in Catania province and the age distribution are similar to those of the rest of Sicily. Roads, including a highway network, and other forms of transportation in and between all provinces are well developed. Medical assistance is also similar across Sicily, as judged by the number of hospital beds and public health expenditure per person. Catania, Messina, and Palermo are the provinces with the largest cities, which contain approximately 60% of Sicilian population, the medical schools, and the major hospitals. In these three provinces, the number of routine biochemical laboratory tests per inhabitant in 2007 was 6.89, 7.42, and 6.18, respectively, indicating that these three areas had similar access to medical assistance (35). Moreover, breast cancer incidence was not statistically significantly different between Catania province and the rest of Sicily (36). The thyroid tumor size distribution was not different between the Catania province and the rest of Sicily. The statistically significant difference in thyroid cancer incidence between Catania province and the rest of Sicily did not change when microcarcinomas were excluded from the analysis (Table 2), and the percentage of

larger tumors, whose detection is much less influenced by advanced diagnostic procedures, was similar among tumors from patients residing in volcanic and nonvolcanic areas.

With so many similarities across Sicily, it was striking that results of the incidence, histotype evaluation, and molecular analysis of thyroid cancers were statistically significantly different between tumors from the Catania province and those from the rest of Sicily. The incidence of papillary cancer was more than twice as high in residents from Catania province than in the rest of Sicily, whereas the incidence of both follicular and medullary cancers was similar in residents from Catania and in those from the rest of Sicily. Moreover, 1.7-fold more papillary thyroid cancers with the *BRAF* mutation V600E were diagnosed in Catania province than in the rest of Sicily.

A possible selective effect of thyroid cancer overdiagnosis in Catania province, therefore, is unlikely because of the reasons indicated above. It is, however, possible that environmental factors in the volcanic area in which most of the population of the Catania province resides may increase the risk of thyroid cancer, as reported previously in other volcanic areas (13–17). In contrast with all previous studies (13–17) in which thyroid cancer incidence was compared with incidence values reported in the literature, our study compared incidence in the volcanic area with that in adjacent nonvolcanic areas in a population of similar ethnicity and lifestyle. Most residents of Catania province obtain their drinking water from the Mt Etna aquifer. The contiguous provinces of Messina and Enna not only receive water from different sources (Figure 1, B) but also are separated from Mt Etna environment by mountainous areas with a low population density. Therefore, it is possible that demographic and orographic factors contribute to the explanation for the negligible influence of the volcanic environment in contiguous provinces.

The mechanism by which a volcanic environment increases the incidence of thyroid cancer is unknown. Active volcanoes produce suspended particulate matter and gases that may contaminate the environment: Many potentially toxic compounds have been detected in various volcanic eruptions and might contaminate cultivated fields and affect vegetable and animal food chains (37). Water samples from the Mt Etna aquifer were found to contain concentrations of several chemicals and elements, including the essential metals iron and manganese, that exceeded the maximum admissible concentrations in drinking water by as much as 50-fold (but that did not exceed the recommended dietary allowance) (38). In addition, the genotoxic and carcinogenic activities of other elements, such as boron and vanadium, are uncertain. In support of the hypothesis that volcanic contaminants contribute to the increased incidence of thyroid cancer in Catania province, none of these chemicals or elements was in excess in the drinking water of two other Sicilian provinces (Palermo and Ragusa) (Table 4). The role of these elements in thyroid carcinogenesis remains unclear because other chemicals pollute volcanic water, although at a lower level.

Mt Etna also releases substantial amounts of ²²²radon, a radioactive gas that is worldwide the largest source of naturally occurring radiation (39). In the Mt Etna area, the concentration of ²²²radon is increased in the environment (40) and in 40% of 119 groundwater specimens examined relative to the maximum allowed

Table 4. Contaminants measured in groundwater sources and tap water in the provinces of Catania, Palermo, and Ragusa (localized in north-east, west and south of Sicily, respectively)*

Element	MAC (µg/L)	No. of specimens with concentrations greater than MAC/total No. (maximum value measured)		
		Catania	Palermo	Ragusa
Boron (B)	1000	131/478 (2100)	0/151 (750)	0/73 (218)
Iron (Fe)	200	92/280 (5300)	6/153 (1380)	1/92 (1330)
Manganese (Mn)	50	87/264 (2600)	3/151 (138)	0/92 (14)
Vanadium (V)	50	193/280 (179)	0/142 (<7)	0/73 (20)
²²² Radon (²²² Rn)†	11	48/119 (57)	–	–

* MAC = maximum allowed concentration.

† Radiation unit in Bq/L [data from D’Alessandro and Vita (21)].

concentration (Table 4) (21). ²²²Radon may cause lung cancer (39), but its effect on the thyroid is not known. Radiation in general is carcinogenic on the thyroid, as shown by the sharply increased incidence of papillary thyroid cancer in Belarus, Ukraine, and Russia after the Chernobyl accident (11). However, in contrast to the high incidence of thyroid tumors with the *BRAF* V600E mutation in Catania province (ie, 55 [52%] of 106 thyroid cancers), the incidence of *BRAF* V600E mutation was low among patients with thyroid cancer who were exposed to radiation from Chernobyl accident (ie, 4%) (41). However, because the carcinogenic effect of ²²²radon on the thyroid is unknown and because the dose of radiation, type of radiation, and length of exposure may differentially affect the molecular profile of radiation-induced tumors and those data were not available for this analysis, we cannot draw any conclusion on the association between increased exposure to ²²²radon and the risk of thyroid cancer.

Some environmental factors, such as industrial pollution and mild iodine deficiency, were not associated with thyroid cancer incidence. Although data on the incidence of thyroid cancer in iodine-deficient areas in our study appear to conflict with previous observations in Sicily in the 1980s (12), the differences might be explained by the facts that different areas were studied (ie, only one-sixth of Sicily was studied previously) and that mild iodine deficiencies in residents of areas with decreased iodine intake have probably been corrected by programmed and “silent” iodine prophylaxis (25,26).

In contrast, thyroid cancer was statistically significantly higher in urban areas than in rural areas, and this increase has been correlated with population density (42). The difference between urban and rural areas was much smaller than that between volcanic and nonvolcanic areas (in which both urban and rural areas are located) and may be explained by a cancer-promoting role of human-derived pollution in urban areas and by the less anthropogenic pollution and slightly different eating and lifestyle habits of rural residents. Moreover, the confounding factor of decreased access to medical care cannot be excluded for rural populations that are present, at the average percentage of 25%, in all provinces of Sicily.

Our study had several limitations. We assumed, but had no evidence, that the composition of volcanic contaminants and their levels found in this study are similar to those in the past. We found

no dose–response association between the level of each measured chemical or element in the water and thyroid cancer disease incidence. This failure may indicate that other unidentified factors (or possibly the same factors in a different combination) may be associated with thyroid cancer incidence. Finally, individual exposures to volcanic contaminants (eg, measurements of water contaminants in biological fluids), the length of residency in a specific district, and the age of individuals at residency were not available.

In conclusion, our data indicate that the volcanic environment of Mt Etna may be a risk factor for thyroid cancer. The striking increase in papillary thyroid cancer incidence that was associated with the Mt Etna volcanic environment leads us to suggest that residents of other volcanic areas (many million people worldwide) could be at increased risk for thyroid cancer and, possibly, of other cancers (eg, *BRAF* mutation–positive melanoma) (43). Although specific risk factors for thyroid cancer in this volcanic environment are still unknown, identification of these factors could help to better understand the cause(s) of the increasing thyroid cancer incidence in the Westernized world and perhaps to develop prevention measures.

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