

Mini Review**The ‘rings of fire’ and thyroid cancer***Leonidas H. Duntas¹, Christos Doumas²¹Endocrine Unit, Evgenidion Hospital, University of Athens, Medical School, Athens, Greece, ²Professor of Archeology, University of Athens, Greece**ABSTRACT**

Several studies have revealed an increased incidence of thyroid cancer in volcanic areas around the world. Hawaii and the Philippines on the rim of the Pacific Ocean, where the greatest number of volcanoes are located at convergent plate boundaries, are among the regions with the highest incidence of thyroid carcinoma worldwide. Iceland is another region also rich in volcanoes in which the highest incidence of thyroid cancer in Europe is found. The common denominator of these regions is their numerous volcanoes and the fact that several constituents of volcanic lava have been postulated as being involved in the pathogenesis of thyroid cancer. This article aims at presenting pertinent data that could link a volcanic environment to thyroid cancer.

Key words: Cadmium, Lava, Selenium, Sulfur, Thyroid carcinoma, Volcanoes

INTRODUCTION

Over the past three decades, the incidence of thyroid cancer (TC) has significantly increased worldwide, rising from a rate of 3.6/100,000 in 1973 to 8.7/100,000 in 2002, without any change in the mortality rate.¹ The increase is almost exclusively due to a rise in papillary cancer rates, this being attributed to both environmental radiation and increased diagnostic scrutiny.² In areas which have not been afflicted by nuclear fallout, the annual incidence of TC ranges from 2.0 to 3.8/100,000 in women and from 1.2 to 2.6/100,000 in men.³

Significant differences in TC incidence have been reported among various regions, with Hawaii, the Philippines and Iceland presenting the greatest incidence worldwide. This phenomenon possibly suggests that common environmental influences in these regions may be responsible for the strikingly high rates.^{4,5} Both Hawaii and the Philippines in the Pacific region as well as Iceland in Europe are characterized by the presence of numerous volcanoes, a fact which indicates that the geographic distribution of TC is possibly related to the topography of the volcanoes. Volcanoes occur in different tectonic settings with the majority located at convergent plate boundaries (such as around the rim of the Pacific Ocean, this particular configuration being known as the ‘Ring of Fire’) where the Earth’s major tectonic plates are moving toward one another. Several other volcanoes

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occur at divergent tectonic plate boundaries such as in Iceland, along the Mid-Atlantic Ridge, along the East African Rift Valley and in the region of the south-eastern Mediterranean, all locations where the plates are pulling apart and magma (molten rock material under the Earth's crust) wells up into the gap, producing volcanoes and lava flows. However, the factors which may account for the geographic distribution and ethnic differences in TC risk have not as yet been defined.

The aim of this article is to review data associating volcanoes with increased incidence of thyroid cancer as well as to briefly describe factors that link volcanoes to TC.

THE PACIFIC RING AND TC

The rim of the Pacific Ocean includes approximately 80% of the Earth's volcanoes (Figure 1). Hawaii, which has the highest reported incidence rate for TC, possesses an efficient tumor registry covering the entire state.⁶ An analysis of data from 1,110 TC

patients residing in Hawaii between 1960 and 1984 and included in the population-based Statistics Epidemiology and End Results (SEER) registry, showed stable incidence rates for TC during this 25-year period. The rates were 8:1 per 100,000 for women and 3:1 per 100,000 for men after age adjustments. The study also revealed a significant variation according to ethnicity, with Filipino women (18.2/100,000) and Chinese men (6.3/100,000) exhibiting the highest rates.⁶

In a study comparing incidence rates of TC among United States-born and foreign-born Filipino, Chinese and Japanese residents of the US, with the rates among US-born Whites, it was demonstrated that Filipino women born in the Philippines had a 3.2-fold higher rate of TC compared to US-born White women.⁷ It is noteworthy that US-born Filipino women were not at increased risk. Moreover, Filipino men born in the Philippines had a 2.6 higher relative risk compared to US-born Filipino men. Thus, the risk of TC among at-risk populations varies by birthplace.⁷ The results of this study clearly show that regions in the Philippines from where residents had migrated to the US are en-

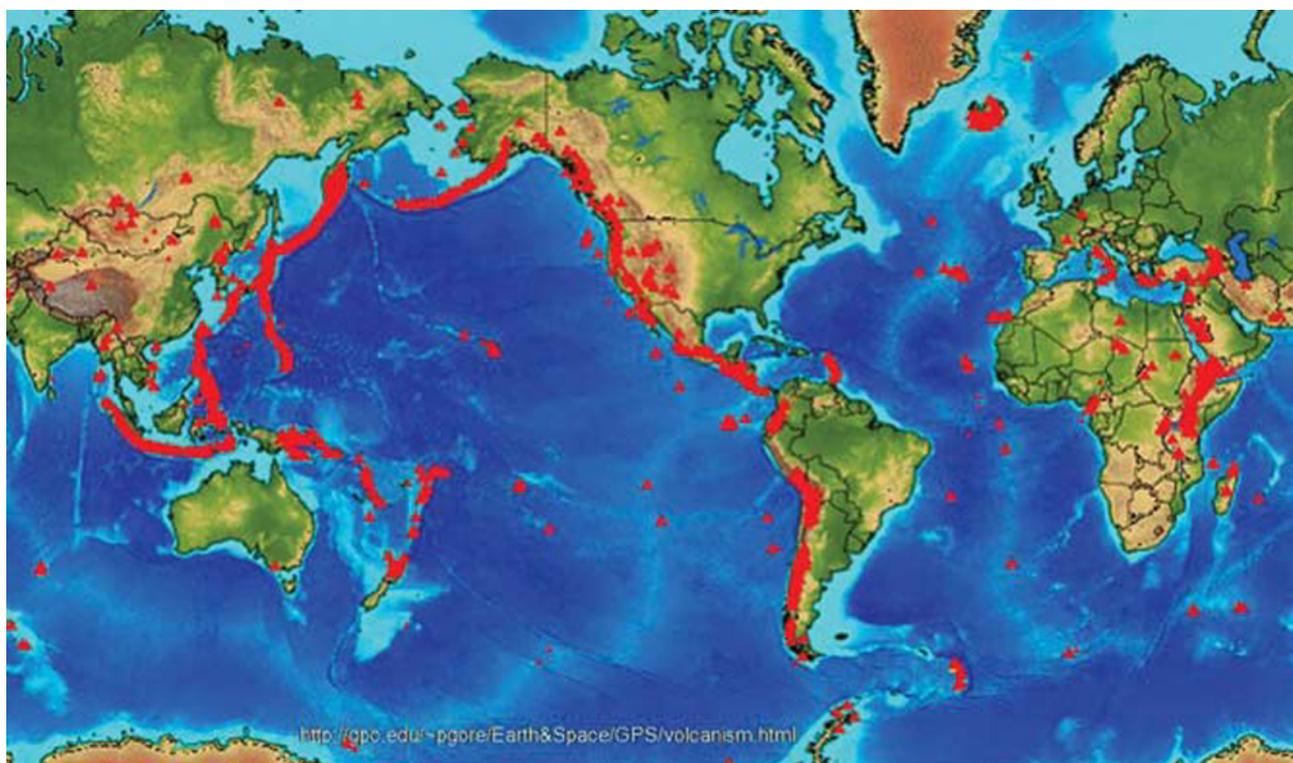


Figure 1. The 'rings of fire': distribution of active volcanoes around the world.

vironmentally 'burdened', exposing the people living in this zone to increased risk for TC. Furthermore, in a retrospective analysis of 72 Filipino patients who were thyroidectomized because of nodular goiter, TC was detected in 69.4% as compared to 38.9% in a group of 72 controls matched for various factors, this underlining the increased risk for thyroid malignancy in Filipino subjects.⁸

Another study conducted in the USA included 7,696 patients with newly diagnosed thyroid cancer reported to the SEER registry between 1973 and 1981.⁹ Striking differences in TC among the various ethnic groups were detected. Thus, Puerto Rico Hispanics and Blacks had significantly lower thyroid cancer rates than New Mexico Hispanic men, Chinese, Japanese, Hawaiian and Filipino men and women. Residents of Hawaii had the highest thyroid cancer rate in the USA, regardless of ethnic group, suggesting that local environmental factors, such as the presence of volcanic lava, together with socio-economic factors may significantly contribute to thyroid tumorigenesis.

THE ATLANTIC-MEDITERRANEAN RING

Volcanoes in Iceland constitute another ring of volcanoes coinciding with the 'colliding' tectonic plate boundaries that extend along the Mid-Atlantic Ridge and the Azores. These become even more dense along the length of the south-eastern part of the Mediterranean Sea and include in particular the volcanoes of Etna and Vesuvius in Italy and the volcano-island of Thera in the Aegean Sea (big and small Kameni in the Caldera), all of which have emerged within the past several millennia. These volcanoes are of the basaltic type characterized by fissured lava and a higher permeable layer.

The annual incidence rate of TC in Iceland is the highest in Europe and among the highest in the world. The Icelandic Cancer Registry reported an incidence for the period 1955-1984 of 4.4/100,000 men and 11.7/100,000 women, a rate that is double that of the other Nordic countries.¹⁰ A 30-year retrospective study on the incidence of TC in Iceland, also encompassing the years 1955-1984 and including 406 registered cases, reported an incidence of 9.5/100,000 for females and 3.4/100,000 for males, which, again and as noted above, is two-fold higher

than in the other Nordic areas.¹¹ Nevertheless, the mortality rates have remained stable during this 30-year period.¹¹ A further analysis of 480 thyroid tumors showed a female-to-male ratio of 2.8 (367 females, 129 males).¹² It is of note that papillary carcinoma accounted for 80% of all thyroid malignancies. The incidence of papillary tumors remains, at a rate of 77%, unusually high, particularly when one considers that the authors have excluded incidentally diagnosed tumors. Cancer of the kidney and CNS tumors were significantly increased in both sexes in all families with papillary thyroid carcinoma.¹³ In the case of Iceland, although both genetic and environmental factors have been implicated, no specific environmental factor(s) which might explain this phenomenon has been identified as yet.¹⁴

The presence of active volcanoes that produce abundant lava has been considered as the common denominator characterizing Hawaii, the Philippines and Iceland. Vanadium, a common trace element that was found increased in the area around Etna, is potentially cytotoxic, especially when zinc and selenium are low.¹⁵ Recently, a metallomics study investigating cancer risk and minerals demonstrated that iodine, arsenic, zinc and sodium are positively correlated, while selenium and vanadium are inversely correlated to cancer, suggesting that these minerals contribute to cancer risk.¹⁶ Vanadium induces COX-2 protein expression in the lung carcinoma cell line via Epidermal Growth Factor (EGF) and the p38 MAPK signaling pathway.¹⁷

Iodine through dietary intake or therapeutically administered can influence the pathogenesis of dif-

Table 1. Trace elements associated with volcanic activity and potentially implicated in thyroid tumorigenesis.

Trace Elements	Status	First Author	Reference
Vanadium	increased	Zwolak I	15
Selenium	decreased	Zwolak I	15
Zinc*	decreased	Zwolak I	15
Iodine	increased	Smyth PPA	17
Cadmium	increased	Yasuda H	16
Sulphur TCN	increased	Varnavas S	18

TCN= thiocyanates

*Zinc concentrations were found highly increased in the hydrothermal waters of Santorini¹⁹.

ferentiated thyroid cancer (DTC).¹⁸ In contrast, iodine deficiency does not appear to be a major factor since the predominant form of TC in the volcanic regions is the papillary subtype which has mainly been associated with iodine excess. Studies on trace metals have not been carried out in the three regions with increased incidence of thyroid CA (Hawaii, the Philippines and Iceland). However, results of studies on trace metals on the volcano-island of Thera may be relevant: notably, zinc levels in the hydrothermal waters ranged from 8 to 56 µg/l.¹⁹ This is an enrichment in Zinc of about 100 fold. Data from studies on Thera published in 1990 showed a cadmium content in hydrothermal waters ranging between 0.5 and 2.3 µg/l, that is, about 7.5 times higher than in seawater. In addition, selenium levels were found significantly decreased in the volcanic waters of Thera as compared to another nearby island without volcanoes (Milos).²⁰ The high content in sulfur and thiocyanates of the peri-volcanic soil might also be involved in thyroid disease as it is known that sulfur, as well as thiocyanate, inhibit iodide transport and organification.²¹ Volcanoes are known to eject large amounts of sulfur dioxide (SO₂). In the region of the Kilauea Volcano in Hawaii, the sulfur dioxide released into the surrounding atmosphere has been associated with cardiorespiratory disease in up to 35% of the residents of this area.²² It has thus been postulated that SO₂ together with other volcanic gases, such as carbon dioxide (CO₂), hydrogen sulfide (H₂S) and hydrogen chloride (HCL), are highly likely to have an acute and chronic impact on health, depending on length of exposure.²³ Furthermore, sulfur competes with selenium compounds for uptake by plants, thereby causing a decrease in selenium availability in the entire ecosystem. As a result, the extensive acidification of the soil following volcanic eruptions, as was recorded for example after the eruption of Etna in 1991, incurs chronic side effects by altering the body's redox-status, affecting the defense mechanisms and leading to inflammation and increasing tumorigenesis.²⁴

Finally, radioactivity is another factor potentially involved in thyroid tumorigenesis in volcanic regions, this assumption being supported by the finding that the presence of a private water-well at one's birth address has been associated with increased risk for papillary cancer.²⁵ Although no investigations have

been conducted as to the factors and mechanisms that lead to increased prevalence of TC in volcanic areas, vigilance amongst the medical community and screening of the population are essential.

CONCLUSIONS

The observed high prevalence of TC around the 'rings of fire' has impelled thyroid experts to increase surveys of and augment investigation into the important issue of a possible relationship of volcanoes to thyroid cancer. Considering the fact that volcanoes are a real threat for over half a billion people living in volcanic regions around the world, efforts must be made to precisely define the mechanisms by which the volcanic environment favors tumorigenesis.

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