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Heavy metals in the volcanic environment and thyroid cancer

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ABSTRACT

In the last two decades thyroid cancer incidence has increased worldwide more than any other cancer. Overdiagnosis of subclinical microcarcinomas has certainly contributed to this increase but many evidences indicate that a true increase, possibly due to environmental factors, has also occurred.

Thyroid cancer incidence is markedly increased in volcanic areas. Thus, the volcanic environment is a good model to investigate the possible factors favoring thyroid cancer.

In the volcanic area of Mt. Etna in Sicily, as well as in other volcanic areas, a non-anthropogenic pollution with heavy metals has been documented, a consequence of gas, ash and lava emission. Soil, water and atmosphere contamination, via the food chain, biocontaminate the residents as documented by high levels in the urines and the scalp hair compared to individuals living in adjacent non-volcanic areas.

Trace amounts of metals are essential nutrients but, at higher concentrations, can be toxic for living cells. Metals can behave both as endocrine disruptors, perturbing the hormonal system, and as carcinogens, promoting malignant transformation. Similarly to other carcinogens, the transforming effect of heavy metals is higher in developing organisms as the fetus (contaminated via the mother) and individuals in early childhood. In the last decades environment metal pollution has greatly increased in industrialized countries. Although still within the "normal" limits for each single metal the hormesis effect (heavy metal activity at very low concentration because of biphasic, non linear cell response) and the possible potentiation effect resulting from the mixture of different metals acting synergistically can explain cell damage at very low concentrations.

The effect of metals on the human thyroid is poorly studied: for some heavy metals no data are available. The scarce studies that have been performed mainly focus on metal effect as thyroid endocrine disruptors. The metal concentration in tissues has been rarely measured in the thyroid. Heavy metal accumulation and metabolism in the thyroid or the carcinogenic activity of different doses and different speciation of metals has not been investigated.

These studies are now warranted to better understand thyroid biology and heavy metal role in human thyroid carcinogenesis.

1. Introduction

1.1. The changing epidemiology of thyroid cancer

Thyroid cancer incidence has dramatically increased in the recent decades (Kilfoy et al., 2009). During the same period no other cancer has increased as much as thyroid cancer.

This striking change has been observed in most industrialized countries, with similar quantitative and qualitative characteristics.

Quantitatively the observed change ranges around +5% per year in the last decade in both women and men (SEER Stat Fact Sheets: Thyroid Cancer, available at http://seer.cancer.gov/statfacts/html/thyro.html accessed on September 10, 2016) while in the same period most malignancies have not increased or, in some instances,

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have shown decreasing incidence (Howlader et al., 2014).

The qualitative changes are also similar worldwide and concern both tumor and host characteristics. Regarding the tumor, most increases are limited to cancers of small size (microcarcinomas, ≤ 1.0 cm maximum diameter) that have reached nearly 50% of newly diagnosed thyroid cancers. Moreover, all or nearly all of the increase concerns the papillary histotype, the least aggressive variant of thyroid cancer.

Regarding the patients, the age-specific curves have greatly changed, with incidence progressively increased in middle-aged individuals and much less in more aged subjects (Vaccarella et al., 2016). Moreover, a gender effect is present with the number of new detected cases much greater in women than in men (Vaccarella et al., 2016).

Considering that thyroid cancer-related mortality rates have not changed substantially during the same period (SEER Stat Fact Sheets: Thyroid Cancer, available at http://seer.cancer.gov/statfacts/html/thyro.html accessed on September 10, 2016), several experts believe that the marked increase of thyroid cancer incidence in the last decades is apparent rather than true, due to the diagnostic emergence of a large reservoir of small, subclinical lesions that are histologically malignant but that might never evolve in a clinical disease able to affect patient health or survival (Davies and Welch, 2014).

While this is by no means a proven hypothesis, indirect evidence is strong and the suggested mechanisms are plausible. Therefore, most experts in the thyroid cancer community believe that increased medical surveillance and wider access to more sensitive diagnostic procedures are the predominant reasons underlying this "thyroid cancer epidemic" that is estimated to increase up to 50–80% the female cases (Vaccarella et al., 2016). The identification of a plethora of asymptomatic nodular lesions of the thyroid that, despite their histological characteristics, should not be considered "malignant" as in most cases they displays stationary or very limited progression (Ito et al., 2010), is causing disproportionate intervention measures with harmful consequences and unjustified costs. These conclusions are shared by the scientific associations that have provided new guidelines to reduce overdiagnosis and overtreatment of thyroid microcarcinomas (Haugen et al., 2015).

Can the overdiagnosis of small cancers that went undisclosed in the past fully explain the striking increase in thyroid cancer incidence recorded in the westernized world in the last 20–25 years? Probably no. Several considerations argue against an exclusive "apparent" increase in thyroid cancer incidence:

- large size cancers, unlikely to be undisclosed in the past, have also increased (Rego-Iraeta et al., 2009; Simard et al., 2012);
- cancer-related mortality has not decreased but it is rather slightly increasing in very recent years (Vigneri et al., 2015), despite earlier diagnosis and more efficacious treatment;
- the pattern of somatic mutations has changed over time even considering only the same histologic variant (Mathur et al., 2011; Romei et al., 2012), which is compatible with the presence of more recent carcinogens
- the increased incidence in pediatric age (when microcarcinomas and incidental tumors are rare) (Vergamini et al., 2014) and the age-specific curves with thyroid cancer increase in middle-aged but not older individuals are also compatible with the recent presence of environmental carcinogens;

Moreover, the increase in incidence paralleling the increase in the diagnostic scrutiny is also parallel with important changes that have occurred in the last decades in the population exposure to potential risk factors. It is possible, therefore, that an aliquot of the increased thyroid cancer incidence is a "true" increase, due to the changing environment and lifestyle.

Indeed, the effects on the thyroid of several changing factors in the environment are not fully appreciated. These factors include the increased exposure to medical radiations, the increase in obesity prevalence in the population, changes in iodine intake, the increasing prevalence of westernized lifestyle, the agroindustry diffusion affecting the diet (with xenobiotics, colorants, preservatives, pesticides, and repellents) and the environment pollution due to industrial products and residues (Marcello et al., 2014). The contribution of some of these "environmental" factors acting as carcinogens in promoting thyroid cancer incidence, therefore, is a poorly investigated possibility.

1.2. Increased thyroid cancer incidence in volcanic areas

The possibility of an association between increased incidence of thyroid cancer and "active volcanoes that produce abundant lava" was first postulated in 1981 (Kung et al., 1981) analyzing cancer registries in the search of environmental carcinogenic agents. In the volcanic islands of both Iceland and Hawaii thyroid cancer incidence was much higher than values in other countries. However, no evidence for a major role of environmental factors related to volcanic activity was provided neither for Iceland, an isolated island with a small population where genetic factors may contribute (Arnbjornsson et al., 1986; Hrafnkelsson et al., 1989) nor for Hawaii where a correlation with dietary factors was observed (Goodman et al., 1988; Kolonel et al., 1990). Very high thyroid cancer incidence was also reported in other volcanic areas as Vanuatu (Paksoy et al., 1989) and in French Polynesia (Curado et al., 2007). Moreover, an incidence 10-fold higher than in most developed countries was reported in New Caledonia, an isolated archipelago located east of Australia in the southwest Pacific (Truong et al., 2007) (Table 1). Values were particularly increased in the Loyalty islands, coral and limestone islands built on top of ancient collapsed volcanoes. Again, genetic factors, lifestyle and environment risk factors were all possible causes. On the basis of these observations it was hypothesized that the geographic distribution of thyroid cancer was related to the geography of volcanoes (Duntas and Doumas, 2009). This possibility was supported by the observation that individuals

Table 1
Incidence rates of thyroid cancer in volcanic areas. The average incidence rate in most countries was $4–5/10^5$ in 1980–1990 and $10–12/10^5$ in the last decade.

Authors	Period of study	Geographical area	Incidence rate	
			Males	Females
Hrafnkelsson et al. (1989)	1955–1984	Iceland	$3.4/10^5$	$9.5/10^5$
Goodman et al. (1988)	1960–1984	Hawaii	$3.1/10^5$	$8.1/10^5$
Paksoy et al. (1989)	1980–1986	Vanuatu	$3.6/10^5$	$9.0/10^5$
Truong et al. (2007)	1985–1999	New Caledonia	$10.4/10^5$	$71.4/10^5$
Curado et al. (2007)	1998–2002	French Polynesia	$5.4/10^5$	$37.4/10^5$
Pellegriti et al. (2009)[a]	2002–2004	Mt.Etna (Sicily)	$6.4/10^5$	$31.7/10^5$

[a] Incidence values in non-volcanic control area in Sicily are $3.0/10^5$ in males and $14.1/10^5$ in females.