The influence of the environment on the development of thyroid tumors: a new appraisal

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Abstract

Most epidemiological studies concerning differentiated thyroid cancers (DTC) indicate an increasing incidence over the last two decades. This increase might be partially explained by the better access to health services worldwide, but clinicopathological analyses do not fully support this hypothesis, indicating that there are carcinogenetic factors behind this noticeable increasing incidence. Although we have undoubtedly understood the biology and molecular pathways underlying thyroid carcinogenesis in a better way, we have made very little progresses in identifying a risk profile for DTC, and our knowledge of risk factors is very similar to what we knew 30–40 years ago. In addition to ionizing radiation exposure, the most documented and established risk factor for DTC, we also investigated the role of other factors, including eating habits, tobacco smoking, living in a volcanic area, xenobiotics, and viruses, which could be involved in thyroid carcinogenesis, thus, contributing to the increase in DTC incidence rates observed.

Key Words
thyroid, oncology, pathogenesis

Introduction

Interpretation of epidemiological data

Papers published during the last 15–20 years relative to the epidemiology of differentiated thyroid cancer (DTC) describe a common phenomenon occurring all over the world, characterized by a steady and continuous increase in the incidence rate of DTC. With only a few exceptions such as Africa (Kilfoy et al. 2009), Sweden, Norway, Denmark (Curado et al. 2007), and The Netherlands (Karim-Kos et al. 2012), almost all data deriving from the Cancer Registries of the USA, Canada, Australia, Europe, and China described more than a doubling of the incidence rate of DTC within the past three decades. Currently, DTC is considered the fastest increasing neoplasia (Howlader et al. 2013), ranking fourth (it ranked 14th as recently as 1990) among the most prevalent cancers. This increasing incidence appears to be so steady that DTC will become the third most common cancer in women of all ages by 2019 (Aschebrook-Kilfoy et al. 2013a). Obviously, due to different genetic factors, environmental influences, and access to medical care, the incidence rates are highly variable among regions; however, this general trend is observed in nearly all instances, independently of the underlying incidence rates (Kilfoy et al. 2009).
The significant increase in the incidence of DTC is mostly attributable to the diagnosis of small (≤ 2 cm) DTCs (Davies & Welch 2006). This may be a consequence of a more intense scrutiny. However, some recent epidemiological studies have indicated that the increased incidence occurred across all tumor sizes and stages (How & Tabah 2007, Chen et al. 2009, Enewold et al. 2009, Rego-Iraeta et al. 2009). Recently, a study carried out in the North American population from 1999 to 2008 has confirmed that the incidence of not only DTCs confined to the thyroid but also those cancers with regional and distant metastasis has increased (Simard et al. 2012).

Another issue concerns the incidence rates of DTC histotypes: a real increase should include all histotypes, whereas almost exclusively papillary thyroid cancers (PTC) have increased, particularly the follicular variant of PTC (FVPTC) (Jung et al. 2014). Follicular thyroid cancers (FTC) have increased very modestly or not at all (Aschebrook-Kilfoy et al. 2013b), and the rates of anaplastic thyroid cancer (TC) are stable or have shrunk (Husson et al. 2013, Pathak et al. 2013). This may indicate the involvement of carcinogenetic factors that influence specific molecular signaling that lead to PTC onset. In fact, there has been mounting evidence, over the recent past decades, of an increasing trend of DTC carrying the BRAF (V600E) mutation – the most frequent genetic aberration associated with PTC (Mathur et al. 2011, Romei et al. 2012). However, two factors may have contributed to the present 8:1 or even higher PTC:FTC ratio: the first one is the change in WHO histotype classification that, since 1988, considers the mixed papillary–follicular histotype a PTC (FVPTC) instead of a FTC; and the second is the correction of the widespread iodine deficiency that, in the past, favored the occurrence of FTCs (Belfiore et al. 1992). More recent data have indicated a sharp increase in RAS mutations due to the increase in FVPTC cases, whereas RET/PTC rearrangements have been decreasing (Elisei 2014). Both BRAF point mutation and RET/PTC chromosomal rearrangement are critical in DTC carcinogenesis, but they are altered via two different mutational mechanisms, as we will further detail, indicating that different etiologic factors are responsible for the observed changes in DTC molecular profiles.

In terms of age at diagnosis, DTC typically occurs in subjects aged 40–50 years, but recent studies have reported that incidence rates are also rising among adolescents and young adults. A recent report from the Italian Cancer Registries (AIRTUM) has documented an increase in the incidence rates among adolescents (15–19 years), with an annual percentage change of +6.1% between 1988 and 2008 (AIRTUM-Workgroup 2013). Similarly, a study analyzing DTC incidence trends in Great Britain among adolescents and adults (0–49 years old) reported a doubling of the number of cases diagnosed during 1976–2005 (McNally et al. 2012). An analogous trend has also been observed among subjects aged 15–39 years old living in Western Australia, where the annual percentage change was +4.0% for females (1982–2007) and +2.1% for males (1982–2000) (Haggar et al. 2012). The increasing incidence of DTC among the young population could indicate the role of other factors in addition to diagnostic screening.

Although access to medical services alone may not be responsible for the increase in the incidence of DTC, it is not a negligible factor. Lee et al. (2012) demonstrated that incidence rates of DTC were inversely proportional to public health expenditure. Countries with a high proportion of private health financing (i.e. private health insurance or patient direct payment) had higher incidence rates of DTC because of the individual’s capability to pay for healthcare services and, therefore, to have more options of diagnostic examinations. Similarly, Morris et al. (2013) reported that, in the USA, the growing rates of DTC incidence are associated with higher levels of healthcare access, leading to the overdiagnosis of indolent cancers that would never be diagnosed. However, socioeconomic status and access to healthcare do not explain the increasing incidence trends of tumors of more than 4 cm observed within the Surveillance, Epidemiology, and End Results (SEER) registry over the past decades (Li et al. 2013).

Data for death rates might be helpful for understanding the reason(s) for this phenomenon. In fact, if cancer incidence rates are really increasing, mortality would also be expected to rise. In contrast, an artificial increase may lead to stable mortality rates (Welch & Black 2010). Unfortunately, available evidence on DTC mortality is quite contradictory. Previous studies documented a stable DTC death rate, at ~0.5 cases/100 000 persons per year (Davies & Welch 2006). In a large analysis of 4187 patients from a single Italian institution, Elisei and colleagues observed that the rate of mortality was reduced for all the clinical, pathological, and follow-up parameters analyzed in the patients who had the disease from 1969 to 1989 (group 1) when compared with patients from 1990 to 2004 (group 2), with the exception of those with distant metastases, who had a poorer outcome regardless of disease development. A possible explanation for these observations is that the treatment and the health care of these patients improved in the last few years, maintaining
very low mortality rates, independent of the initial stage of disease (Elisei et al. 2010). However, recent data from the SEER show that DTC mortality has been significantly increased during the last decades, mostly in males. The annual percentage change (APC) for mortality was +0.5% for females from 1988 to 2010 (−2.7% during the period 1975–1988) and +1.2% for males from 1983 to 2010 (−3.1% during the period 1975–1983) (Howlader et al. 2013). Nevertheless, these data are difficult to interpret, as DTC progresses very slowly, and the effect on mortality of a truly increased incidence may become evident only after decades of follow-up.

Despite an increasing understanding of the biology and molecular pathways underlying thyroid carcinogenesis, our knowledge of the documented risk factors for the disease is very similar to what we knew 30–40 years ago.

In this paper, we aimed to review current knowledge of well-known DTC risk factors, such as ionizing radiation exposure, and to investigate the role of other factors, including eating habits, tobacco smoking, living in a volcanic area, xenobiotics, and viruses, which could be involved in thyroid carcinogenesis and eventually influence the increase in DTC incidence rates observed.

Environmental factors and their relationship with thyroid cancer

Radiation exposure

The most robust and well-accepted risk factor for DTC is exposure to ionizing radiation, which increases the risk of thyroid malignancy from 5 to 50% (Robbins et al. 1991). The first association between DTC and radiation was observed in 1950, in children who received X-ray therapy in the thymus (Duffy & Fitzgerald 1950). Ron et al. (1995) reviewed seven studies and concluded that both external radiation (X-ray and γ-radiation) and internal exposure to radioiodine (by inhalation or ingestion) could increase the risk of thyroid cancer. Results from a series of further studies have demonstrated an increased incidence of thyroid tumors in children after external radiation for the treatment of different benign conditions of the head, neck, and thorax (Winship & Rosvoll 1970). The atomic bomb explosions in Japan in 1945 (Nagataki et al. 1994), the radioactive contamination of the Marshall Islands in 1954 (Cronkite et al. 1995) and Chernobyl radioactive fallout accident in 1986 (Kazakov et al. 1992, Tuttle & Becker 2000, Williams 2002) provided solid evidence of the effects of environmental radiation exposure (Parker et al. 1974, Imaizumi et al. 2006). These effects include multiple DNA injuries due to concentration of radioactive iodine in the gland, leading to the deregulation of cell growth and proliferation (1993) coupled with an impaired ability of T-cells to fight cancer cells, allowing them to multiply (Yarilin et al. 1993) (Fig. 1).

Sporadic PTC developed post-Chernobyl are characterized by constitutive activation of effectors along the RAS–RAF–MAPK signaling pathway, and the most frequent genetic alterations are rearrangements of the RET/PTC gene. The prevalence of these alterations differs in adult and pediatric tumors: in adults, RET/PTC rearrangements are found in more than 30% of thyroid tumors, whereas in children, RET/PTC rearrangements correspond to 60–80% (Fugazzola et al. 1995, Klugbauer et al. 1995, Cohen et al. 2003, Soares et al. 2003, Lima et al. 2004). In addition, a BRAF chromosomal rearrangement (AKAP9–BRAF) was described in 10% of radiation-induced PTC (Thomas et al. 1999, Ciampi et al. 2005).
A high prevalence of \textit{RET/PTC} has also been found in patients submitted to X-ray radiation therapy (Bounacer et al. 1997, Collins et al. 2002). This rearrangement is the most common and comprises more than 90% of all rearrangements found in radiation-induced sporadic tumors, the most frequent ones being \textit{RET/PTC1} and \textit{RET/PTC3} (Caudill et al. 2005). \textit{RET/PTC1} rearrangement is a fusion of \textit{RET} tyrosine kinase region with the 5’-end region of H4/D10S170 (CCDC6). \textit{RET/PTC3} occurs through the fusion of RFG/ELE1/ARA70, on chromosome 10, where there is a paracentric inversion (10q11.2–10q21; Santoro et al. 1994, 2006). Hamatani et al. (2008) have shown that \textit{RET/PTC} rearrangement had a direct correlation with increased radiation dose, while \textit{BRAF} mutation was inversely correlated with dose exposure.

Although rearrangements such as \textit{RET/PTC} and AKAP9–BRAF are relatively common in radiation-exposed individuals, point mutations in \textit{BRAF} and \textit{RAS} are rare and inversely correlated with radiation doses. These mutations were found in elderly patients who were exposed to low doses of radiation, or in atomic bomb survivors, corroborating the current concept that \textit{BRAF} and \textit{RAS} mutations are part of cellular malignant transformation induced by intracellular factors, and not by external factors such as radiation (Kimura et al. 2003, Hamatani et al. 2008, Nikiforov & Nikiforova 2011).

Yang et al. (1997) demonstrated an increase in dose-dependent changes in p53 levels after exposure of a normal thyrocyte to radiation, accompanied by DNA repair in vitro. Another study showed a lower number of \textit{ARG} genotype homozygous \textit{TP53} alleles in PTC adult patients exposed to radiation when compared with sporadic PTC patients and indicated that combinations of alleles can contribute to \textit{TP53} DTC risk in individuals exposed to radiation during childhood, adolescence, or even adulthood (for women; Rogounovitch et al. 2006). However, mutations in \textit{TP53} may not be used as a marker of radiation-induced disease. This is due to the fact that \textit{TP53} mutations and polymorphisms are frequent in both radiation-induced PTC and sporadic tumors (Hillebrandt et al. 1996, Nikiforov et al. 1996, Suchy et al. 1998, Rogounovitch et al. 2006). Our group, for instance, has demonstrated that non-radiation-exposed patients with FTC and PTC had a higher frequency of codon 72 polymorphic genotypes when compared with a control population. The inheritance of these genotypes was associated with a significantly higher risk of FTC (OR=9.714) and PTC (OR=5.299) development (Granja et al. 2004a). In another study, we further demonstrated that \textit{TP53} expression was common, mainly in early stage DTC, as expected from a tumor suppressor gene (Marcello et al. 2013).

\textbf{Iodine and eating habits}

Iodine intake may influence the incidence and prevalence of thyroid disease in general and of thyroid cancer in particular (Wartofsky 2010). There are no doubts that the increase in iodine intake all over the world has influenced the epidemiological scenario of DTC. However, the role of iodine intake in the increasing incidence of thyroid cancer is still a matter of debate. In fact, iodine deficiency is associated with an increased risk of FTC, whereas chronically high iodine intake may increase the risk of PTC (Knobel & Medeiros-Neto 2007). Biographical data, tumor characteristics, and treatment and outcome for 190 patients with DTC from 1970 to 2000 were reviewed retrospectively by Dijkstra et al. (2007). They found a significant increase in the incidence of PTC, which may be related to increasing dietary iodine intake. Conversely, inadequate low iodine intake will result in increased thyroid-stimulating hormone (TSH) stimulation, increased thyroid cell responsiveness to TSH, increased thyroid cell epidermal growth factor-induced proliferation, decreased transforming growth factor beta 1 (TGF\(b\)1) production and increased angiogenesis, all phenomena related to promotion of tumor growth (Knobel & Medeiros-Neto 2007; Fig. 2).

Cardis et al. (2005) carried out a population-based case–control study in Belarus and the Russian Federation aiming to investigate environmental and host factors that may modify the risk of DTC after childhood exposure to radioactive iodine. The risk of radiation-related DTC was three times higher in iodine-deficient areas than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk of radiation-related DTC by a factor of three, indicating that both iodine deficiency and iodine supplementation modify DTC risk. In fact, stable iodine given shortly before, during, or immediately after exposure, may reduce the uptake of radioactive iodine by the thyroid gland, leading to a decrease in the radiation dose delivered to the thyroid (Nauman & Wolff 1993, Zannonico & Becker 2000). This effect has important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of DTC related to radioactive iodine in the event of exposure during childhood, which may occur after radiation accidents or during medical diagnosis and therapeutic procedures (Cardis et al. 2005).
Guan et al. (2009) compared the prevalence of T1799A BRAF mutations in 1032 classic PTC patients from five regions of China that have different iodine contents in natural drinking water, ranging from normal to high. The prevalence of BRAF mutations was significantly higher in high-iodine content regions when compared with normal-iodine-content regions, indicating that high-iodine-intake is a significant risk factor for the occurrence of BRAF mutations and may, therefore, be a risk factor for PTC development (Guan et al. 2009).

Recently, Fuziwara & Kimura have demonstrated that iodine exerts protective effects on thyroid cancer cell lines, attenuating acute BRAF oncogene-mediated microRNA deregulation (Fuziwara & Kimura 2013). This result may explain the mechanism through which excess iodine inhibits thyroid follicular cell proliferation associated with TGFβ pathway activation (Fuziwara & Kimura 2013). Fiore and colleagues studied PTC3–5 cells, a rat thyroid cell lineage harboring the Ret/Ptc3 translocation. The cells were treated with iodine and cell growth was analyzed. A significant inhibition of proliferation was observed in iodine-treated cells, along with no significant variation in cell death rate. Furthermore, iodine treatment attenuated the loss of NIS and TSHR gene and protein expression induced by Ret/Ptc3 oncogene induction. In addition, iodine treatment reduced RET and ERK phosphorylation, without altering BRAF and ERK expression, indicating an antioncogenic role for iodine excess during thyroid oncogenic activation (Fiore et al. 2009).

In addition to iodine intake, other macro- and micronutrient factors may modify DTC risk. In a recent publication, our group has reported that women with excess weight (BMI > 25 kg/m²) were at higher risk of developing DTC, and although these individuals consumed excess carbohydrate, protein, and fat in comparison with eutrophic subjects, only excess carbohydrate and protein were related to DTC risk (Marcello et al. 2012). The association between carbohydrate and DTC risk is possibly related to the secondary effects of excess carbohydrate accumulation, i.e. insulin resistance (IR). In fact, Rezzechino et al. (2008, 2009a,b) have demonstrated in a series of studies that patients with thyroid nodules

**Figure 2**
Schematic figure representing the relationship of food and drinks with DTC. Iodine has long been known to modify thyroid hormones levels, inducing systemic changes that will lead to DTC. Also, macronutrients such as carbohydrates and proteins, when metabolized, generate other compounds that may lead to the development of DTC.
and, more specifically DTC, presented higher frequencies of IR when compared with controls. Although these authors did not present evidence relating dietary intake and IR, it is well known that a carbohydrate-rich diet is a potential risk factor for the development of IR (Heer & Egert (In Press)). Furthermore, the accumulation of carbohydrate and the impairment of insulin regulation might lead to a deregulation of the PI3K/AKT pathway, which has been strongly related to DTC development and progression during recent (Gomez Saez 2011, Nikiforov & Nikiforova 2011, Bartholomeusz & Gonzalez-Angulo 2012), favoring disorganized cell growth and proliferation, thus leading to an increased risk of DTC.

The increased risk of DTC related to the excess protein consumption reported by our group is controversial. Truong et al. (2010) did not find any relationship between consumption of saltwater fish, canned fish, or seafood and thyroid cancer risk. Similarly, Bosetti et al. (2001) did not prove any association between DTC and fish or shellfish consumption. Other cancers, such as breast, prostate, and colon, have already been related to excess protein consumption, and although the mechanisms involved in this relationship are not fully understood, one of the possible explanations is that the high nitrosamine content of some processed meat products may increase the risk of developing cancer (Allen et al. 2012). In fact, results from recent studies have indicated that the intake of nitrite and nitrate through drinking water or food intake might increase the risk of DTC (Kilfoy et al. 2011, Hinther et al. 2012, Aschebrook-Kilfoy et al. 2013c). Once in the stomach, nitrite reacts with amines, amides, or amino acids and produces N-nitroso compounds, very important carcinogens for animals (Mirvish 1995). Nitrate, in turn, competes with iodine and may inhibit iodine uptake, affecting thyroid hormone production, which might lead to a stimulation of thyroid growth and tumor formation (Tonacchera et al. 2004, De Groot et al. 2006).

Other authors have suggested that dairy protein may increase circulating concentrations of insulin-like growth factor 1 (IGF1; Crowe et al. 2009). This factor could be related not only to proteins but also to carbohydrates, as its regulation depends on glucose and insulin availability as well, but more functional studies are necessary to better characterize how dietary patterns would affect IGF1.

**Tobacco smoking**

Smoking is a well-known risk factor for many types of cancer, but studies in DTC are still controversial. According to the Centers for Disease Control and Prevention (CDC), tobacco smoke contains a mixture of more than 7000 chemicals. Hundreds of chemicals are toxic, and approximately 70 can cause cancer (CDC 2010). The three main classes of carcinogens are polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and tobacco-specific nitrosamines (Bartsch et al. 2000). The mechanism through which PAHs, such as benzopyrene, interact with DNA, activate oncogenes, and initiate the carcinogenic process involves the formation of carcinogens. Benzopyrene is converted into phenolic metabolites in a reaction mediated by cytochrome P450 (CYP) enzyme, responsible for metabolizing toxic substances (Coles & Ketterer 1990).

A secondary step involving other forms of CYP is responsible for the formation of more toxic reagents. Conversely, several carcinogens present in tobacco smoke are converted into hydrophilic substances by glutathione S-transferases (GST), mainly GSTM1 and GSTP1, responsible for the detoxification of these substances in the organism (Coles & Ketterer 1990).

Although several studies have tried to establish the relationship between smoking and DTC, their results are rather conflicting and confusing. A large cohort study with 3.869 patients presenting thyroid diseases showed that smoking women had higher prevalence of nontoxic goiter and diffuse toxic goiter when compared with nonsmoking women. TSH concentration was significantly lower in smokers than in ex-smokers and nonsmokers, but not triiodothyronine (T3) concentrations (Ericsson & Lindgarde 1991). Sokic et al. (1994) identified cigarette smoking as a risk factor for thyroid cancer (RR = 7.12; 95% CI = 1.53–32.99), in addition to five other factors: family history of any malignant tumors, history of goiter or thyroid nodules, long-term occupational exposure to chemicals, history of second primary tumors, and diagnostic X-ray exposure. However, more recent studies have indicated an inverse relationship between cigarette smoking and DTC. Rossing and colleagues studied the association between smoking habits and DTC in 558 women with PTC and observed that patients who smoked more than 100 cigarettes were at a reduced risk of developing DTC, especially if they were current smokers (OR = 0.5; 95% CI = 0.4–0.7). The authors suggested that smoking reduces thyroid cell proliferation by exerting effects on TSH, estrogen, or other mechanisms (Rossing et al. 2000).

In 2003, Mack and colleagues published a pooled analysis of 14 case-control studies of different ethnic groups regarding cigarette smoking and the consumption of alcohol, tea, and coffee. They found that DTC risk was reduced by 40% among smokers with PTC and FTC, indicating that cigarette smoking exerts a protective effect against the development of DTC (Mack et al. 2003).

Some authors have suggested that there are relationships among smoking habits, genetic profile, and DTC susceptibility. In fact, our group was the first to demonstrate an inverse association between WT CYP1A1 m1 gene inheritance and smoking with reduced susceptibility to thyroid nodules, especially PTC (Bufalo et al. 2006). After that, Kiseljak-Vassiliades & Xing (2011) found an association between smoking habits and RARβ2 aberrant methylation, in PTC. Aschebrook-Kilfoy et al. (2012) also found a significant association between three polymorphisms of CYP26B1 gene (rs975612, rs11681809, and rs194243) and cigarette smoking. The influence of BRAF and RAS genes in thyroid tumors is widely known. Zhang et al. (2013) showed that the inheritance of polymorphisms of the BRAF gene (rs1042179) increases PTC susceptibility among smokers. On the other hand, Khan et al. (2013) verified that nonsmokers were more significantly associated with polymorphic genotypes T81C of the HRAS gene (n=76 in cases and n=17 in controls; OR=6.4; 95% CI=2.4–16.4; P<0.05), while individuals who were or had been smokers showed insignificant association (P>0.05) (Zhang et al. 2013).

Other studies did not detect correlations between smoking habits and the risk of DTC (Ron et al. 1987, Kreiger & Parkes 2000, Bandurska-Stankiewicz et al. 2011). There are reports of a negative association between smoking habit and obesity in the risk of thyroid cancer (Guignard et al. 2007, Kitahara et al. 2011, Han et al. 2013). A report relating different associations between smoking and thyroid function and size showed an increased risk of Graves’ disease (GD; Graves’ hyperthyroidism and Graves’ ophthalmopathy) and nontoxic goiter (multinodularity) and a decreased risk of Hashimoto’s disease (thyroid antibodies and autoimmune hypothyroidism) and DTC (PTC and FTC) (Wiersinga 2013).

In this scenario, although more recent studies with large cohorts have indicated an inverse correlation between DTC and tobacco consumption, we still do not understand the effects of the many toxic compounds found in cigarette smoke on DTC.

**Volcanic areas**

Some of the highest DTC incidences worldwide were observed among people living in volcanic areas such as Iceland (Ambjørnsson et al. 1986), Hawaii (Kolonel et al. 1990), French Polynesia (Curado et al. 2007), New Caledonia (Truong et al. 2007), and Sicily (Pellegriti et al. 2009). In 1970, a 5-year study revealed the incidence of thyroid cancer in Oahu, Hawaii, to be the highest in the world in women and among the highest in men (Haber & Lipkovic 1970). Kung et al. (1981) reported that the presence of active volcanoes which produce abundant lava was the common denominator of Iceland and Hawaii, where the incidence of thyroid cancer is outstandingly high. He postulated the presence of a carcinogenic agent in the lava and also that the unexceptional incidences of thyroid cancer found in the volcanic areas of British Columbia, Japan, Cali, and Colombia were caused by differences in the type of underlying volcanoes. While Iceland and Hawaii have ‘basaltic low-viscosity’ volcanoes with productive lava flows, the other areas have the ‘Strombolian’ type of eruptions that are highly viscous and produce minimal flows. He also emphasized the interest of possible differences (Favalli et al. 2004) if the composition of the soil, which ultimately develops from these flows, was found to differ from the soils in other regions of the world (Kung et al. 1981). Goodman et al. (1988) reported thyroid cancer incidence in Hawaii, showing a significant variation on the basis of ethnicity, with the highest rates occurring in Filipino women (18.2/100 000) and Chinese men (6.3/100 000). Hawaii residents generally had much higher rates, indicating that environmental influences were responsible for the unusually high incidence rates in Hawaii.

Geological processes such as volcanism may concentrate certain elements, even to unhealthy levels. Some trace element metals such as fluorine, manganese, iron, copper, zinc, selenium, and iodine are present in very low quantities in our bodies and are important for life functions. There are approximately 100 naturally occurring elements, many of which are toxic to humans at high doses (Kusky 2003). Active volcanoes produce suspended particulate matter and gases: sulfur dioxide, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, hydrochloric acid, sulfuric acid, ammonium sulfate, helium, and radon. Many potentially toxic compounds, detected in various volcanic eruptions, might contaminate cultivated fields and affect the vegetable and animal food chain (Hansell & Oppenheimer 2004, Hogan & Bearden 2007). Trace elements associated with volcanic activity are potentially implicated in thyroid tumorigenesis (Duntas & Doumas 2009).

Based on the previous reports on volcanic areas, recently a 3-year epidemiological survey from the Sicilian Regional Registry for Thyroid Cancer (SRRTC) collected data on all incident thyroid cancers in Sicily (the biggest island in the Mediterranean, with almost five million inhabitants distributed in nine provinces) and their...
associations with different environmental factors. Particularly, the incidence of thyroid cancer in the Catania province, where most residents live in the Mount Etna volcanic area, has been evaluated and data have been compared with those from adjacent nonvolcanic areas of Sicily (Pellegriti et al. 2009). Over the course of 3 years, 2002–2004, 1950 incident thyroid cancers were identified. The incidence of thyroid cancer was 2.3-fold higher in the province of Catania with an age-standardized rate of 31.7/100 000 in females and 6.4/100 000 in males, vs 14.1 and 3.0, respectively, in the other non-volcanic provinces of Sicily ($P$<0.0001). The incidence of thyroid cancer was different neither between the industrial and the non-industrial areas nor between the areas of sufficient and deficient iodine intake. The papillary but not follicular or medullary histotype was significantly more prevalent in the Catania province ($P$<0.0001; Pellegriti et al. 2009).

Mount Etna is a large basaltic volcano with fissured and highly permeable lava layers interbedded with discontinuation layers of scarcely permeable pyroclastics. The main aquifers of Etna lie at the contact between the volcanic rocks and the underlying impermeable sediments. An active geothermal system with estimated temperatures of 100–150 °C is hosted in the underlying sedimentary sequence. At high temperature, many minerals are solubilized and an enormous amount of CO$_2$ produced by the volcanic degasification leads to the acidification of water and chemicals leaching from the basalt rock (Brusca et al. 2001, Malandrino et al. 2013).

The Mount Etna aquifer, which provides drinking water to the large majority of Catania province residents, had a variety of elements exceeding the maximum allowed concentration (MAC) fixed by the European and National regulations. Among these were essential elements such as iron and manganese and also chemicals such as boron and vanadium, the genotoxic and carcinogenic activity of which are uncertain (Giammanco et al. 1996, Roccaro et al. 2007). None of these elements was found in excess in the drinking water of two other Sicilian provinces (Pellegriti et al. 2009). Vanadium exceeding the MAC is classified by the International Agency for Research on Cancer (IARC) as a possible human carcinogen (group 2B; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2006), which may influence thyroid function and cell proliferation. Experiments on rats documented the role of vanadium in affecting iodine metabolism and thyroid function by decreasing the thyroid peroxidase activity (Uthus & Nielsen 1990).

Other trace elements which can act as thyroid disruptors are fluorine, sulfur, and selenium. Fluorine: Volcanoes represent the main natural persistent source of fluorine (mostly in the form of hydrogen fluoride). Mount Etna is the largest known point source of atmospheric fluorine, even stronger than today’s total estimated anthropogenic release over Western Europe. Volcanic rocks contain high levels of fluorine, which are transferred to groundwaters (D’Alessandro 2005). Administration of excessive fluorine has been related to thyroid dysfunction (Jooste et al. 1999, Wang et al. 2009). While natural sources of selenium include soil, plants, microorganisms, animals, and sea salt, volcanoes also comprise a significant source of selenium. Sulfur, also emitted by volcanoes, has an interesting relationship with selenium and shares many of its chemical properties: sulfur competes with selenium compounds for uptake by plants, causing a decrease in available selenium. Volcanic eruptions can affect the distribution and availability of both sulfur and selenium. As a constituent of selenoproteins, selenium has structural and enzymatic roles, in the latter context being best known as an antioxidant and catalyst for the production of active thyroid hormone (conversion of thyroxine (T$_4$) to T$_3$ peripherally). Selenium deficiencies may impair thyroid function (Rayman 2000).

Volcanoes are also ‘emitters’ of trace elements and, in addition to water, volcanic eruption products may contaminate the environment through volcanic ash and gases. Metals separated from the magma during degassing are transported by rising gases, and as they approach the surface, they condense into small particles that are dispersed throughout the atmosphere (Hansell & Oppenheimer 2004). Most commonly, winds in the Mount Etna region blow from the north to northwest (Favalli et al. 2004). The Mount Etna plume, therefore, moves mainly towards the south-east, and Catania province inhabitants mostly live in the downwind areas of the ash fallout. Therefore, these individuals are exposed to high levels of these particulates. Moreover, vegetables and plants may accumulate various trace elements dispersed in the atmosphere (Malandrino et al. 2013). Several studies have documented an increased amount of heavy metals in plants grown in volcanic areas. Vegetable contamination may occur not only through the atmospheric pollution but also as a result of the presence of heavy metals in the irrigation water (Dahal et al. 2008). Similar findings were reported in studies of water samples from other volcanic areas (Tilling & Jones 1996, Martin-Del Pozzo et al. 2002, D’Alessandro 2005).

Mount Etna also releases significant amounts of $^{222}$Radon gas. Radon is a poisonous gas that is produced as a radioactive decay product of the uranium decay series. Its concentration has been found to be increased both in the
environment and in 40% of 119 groundwater specimens in the area around Mount Etna (D’Alessandro & Vita 2003).

Other recent studies have reported a high incidence of thyroid cancer in volcanic areas (Duntas & Doumas 2009, Biondi et al. 2012). A more recent Icelandic study showed that populations residing in geothermal hot-water supply areas have a higher risk of developing cancer (HR 1.15) as compared with residents living in nongeothermal areas. Positive exposure-response relations were observed between the risk of cancers and the degree of volcanic/geothermal activity in the reference areas. Increased incidence of all types of cancers was found in populations using geothermal hot water for decades (Kristbjornsdottir & Rafnsson 2013).

Finally, environmental carcinogens of volcanic origin could be responsible for gene mutations favoring thyroid carcinogenesis, such as the higher rate of BRAF (V600E) mutation in eastern Sicily (hosting Mount Etna), when compared with western Sicily (Frasca et al. 2008).

Observations in volcanic areas indicate that environmental carcinogens present in the atmosphere, soil, or water promote PTC and that the volcanic environment is one of the risk factors for thyroid cancer (Fig. 3). Millions of people are exposed to volcanic environments worldwide with more than 1500 active volcanoes. The specific etiological agent has not yet been identified. Additional studies are also necessary to ascertain whether, in addition to thyroid cancer, other cancers are favored by the volcanic environment, for example there is an increased incidence of mesothelioma in the Biancavilla municipality district in the Mount Etna area (Comba et al. 2003) or in endemic Kaposi’s sarcoma in Africa (Ziegler 1993).

Xenobiotics

Xenobiotics are exogenous compounds and chemicals that interfere with the biological functions and the homeostatic maintenance of the human organism. These substances may
originate from natural sources (plants and bacteria), but most of them are derived from human activities because of their application, such as flame retardants, pesticides, repellents, or thermal insulators. These compounds are also called persistent organic pollutants because they are not degradable, accumulate in the environment, and as part of the food chain, may be absorbed by humans and wildlife. Therefore, people are largely exposed to xenobiotics that may influence human health, even exerting a carcinogenic effect when they are not metabolized by detoxification enzymes (Fig. 4). Xenobiotics are able to bind cell membrane receptors, acting as either agonists or antagonists, influencing receptor–ligand binding and modulating receptor expression. Some compounds may be transported into the nucleus where, through binding with nuclear receptors, they form DNA-binding units that influence gene expression. These interactions may also cause epigenetic modifications (i.e., DNA methylation and histone acetylation) that eventually regulate gene functions.

Concerning the endocrine system, xenobiotics act mainly as disrupting chemicals (endocrine-disrupting chemical (EDC)) that influence the physiological functions and the hormone production of several endocrine glands. The thyroid is one of the most affected glands. Thyroid function may be disrupted in different ways (Pearce & Braverman 2009): perchlorate and nitrate are competitive inhibitors of the sodium/iodide symporter (Lawrence et al. 2000, Dohan et al. 2007); isoflavones inhibit TPO activity (Divi et al. 1997); polybrominated diphenyl ethers (PBDE) inhibit binding of thyroid hormones to transport proteins (Kawano et al. 2005); PBDE and bisphenol A (BPA) bind to thyroid hormone receptors (Marsh et al. 1998, Moriyama et al. 2002); styrenes inhibit peripheral deiodinase activity thus preventing the conversion of T4 to T3 (Santini et al. 2008); PBDE and dioxins decrease the half-life of T4 life in serum by inducing the activity of hepatic uridine diphosphate glucuronosyltransferases (UDPGTs), which glucuronidate T4 (Zhou et al. 2001, Emi et al. 2007).

All these mechanisms explain the reason why people exposed to these compounds may have decreased serum concentrations of T4, and increased TSH values, and are affected frequently by autoimmune thyroid disorders. However, it has not yet been clarified whether xenobiotics
may promote thyroid carcinogenesis. Hypothetically, the chronic stimulation from elevated TSH values and the autoimmune inflammatory processes may cause proliferative changes in the thyroid follicular epithelium, favoring cell hypertrophy and hyperplasia, as well as the onset of thyroid cancer (Capen 1997). Obviously, not all subjects exposed to potential carcinogens will develop thyroid cancer. Carcinogens, such as PBDE and other polyhalogenated aromatic hydrocarbons, are generally metabolized and then inactivated by a variety of xenobiotic-metabolizing enzymes (CYP family, epoxide hydrolase, glutathione transferase, etc.). The individual’s susceptibility to thyroid cancer initiation, promotion, and progression may be explained in part by a malfunctioning detoxification process secondary to polymorphisms of the genes encoding components of the above-mentioned metabolic pathways (Siraj et al. 2008, Zhang et al. 2008).

BPA is the most studied EDC. It is the main constituent of polycarbonate plastic and it is calculated that every year over 100 tons of BPA are released into the atmosphere (Burridge 2003). Humans are, therefore, ubiquitously exposed to BPA through sources that are not always completely understood, and BPA disrupts thyroid mechanisms that are not yet well known. It seems to be a selective antagonist of the thyroid hormone receptor β isoform (Zoeller et al. 2005), and recently it has been documented that in an in vivo model (zebrafish) BPA appeared to alter the expression of both genes involved in thyroid hormone synthesis and thyroid-specific transcriptional factors (Gentilcore et al. 2013). At present, however, no relationship between thyroid cancer and BPA exposure has been demonstrated.

Other studies reported that workers of certain categories, who are frequently exposed to one or more chemicals, had an increased risk of thyroid cancer. Women working in shoe-manufacturing units in Sweden and probably exposed to different mixtures of solvents had a high risk of developing thyroid cancer (Lope et al. 2009). Similarly, among women textile workers, in Shanghai, thyroid cancer was associated with a potential exposure period lasting more than 10 years to benzene (HR = 6.4; 95% CI = 1.1–38), organic or inorganic gases (HR = 7.7; 95% CI = 1.1–51), and formaldehyde (HR = 8.3; 95% CI = 1.2–60) (Wong et al. 2006). A Canadian case-control study reported a higher risk of thyroid cancer among workers in the wood, pulp, and papermaking processing (OR = 2.54; 95% CI = 1.11–5.83), as well as sales and services (OR = 1.26; 95% CI = 1.05–1.52) (Fincham et al. 2000).

Polluted atmosphere, water, and soil may be causes of human contamination. In fact, a high incidence of thyroid cancer has been reported in Spain among people exposed to hexachlorobenzene, as a consequence of living near an organochlorine compound factory (Grimalt et al. 1994). Intake of nitrate, which commonly contaminates drinking water and vegetables because of its use as fertilizer, has been associated with the risk of thyroid cancer (Aschebrook-Kilfoy et al. 2012). This risk is increased significantly with the increase in both nitrate concentration in public water supplies and duration of consumption of nitrate-contaminated water (Ward et al. 2010).

In a recent study, Jung et al. (2014) have detected indications that the increasing incidence of DTCs is also accompanied by a change in the molecular profile of these cancers: the analyzed cases showed a significant increase in PTC cases presenting BRAF and/or RAS mutations and a noticeable decrease in those presenting RET/PTC rearrangements. Considering that RET/PTC rearrangements were very common in radiation-induced tumors, it is understandable that once the radiation exposure diminished or stopped, the number of patients presenting these rearrangements also decreased. Concerning BRAF mutations, and more specifically BRAFV600E point mutation, the marked increase observed may be related to exposure to chemicals, because a higher prevalence of the BRAFV600E mutation has been reported in China and Sicily, both regions very rich in chemicals such as nitrites, nitrates, boron, iron, manganese, and vanadium in drinking water (Guan et al. 2009, Pellegriti et al. 2009). Thus, it is possible to propose the hypothesis that an overexposure to chemicals may be the reason for the increase in BRAF-mutated cases observed all over the world.

Furthermore, it is well known that people who are exposed to xenobiotics, either because they belong to some specific categories of workers, or because they live in polluted areas, and who carry a polymorphism involving xenobiotic-metabolizing genes, have a higher risk of cancers. Although BRAF mutation might be associated with chemical exposure, we still do not understand the molecular mechanisms possibly involved and further investigations are needed in order to prove this association.

**Metabolization and detoxification systems**

Most xenobiotics require metabolic activation before binding to DNA, RNA, and protein. Therefore, variations in the activation and detoxification processes play an important role inorganic responses to xenobiotics (Bartsch & Hietanen 1996). A balance disorder of these processes...
may explain the variability in individual’s responses to exposure to such compounds (Anwar et al. 1996).

There are two forms of metabolism for toxic compounds: the metabolism mediated by oxidases – phase I and that mediated by conjugating enzymes – phase II, and they may lead to the activation or inactivation of xenobiotics (Bois et al. 1995). Many compounds, such as PAHs, nitrosamines, and drugs, are converted into highly reactive oxidative metabolites by phase I enzymes, a group mainly constituted by members of the CYP family (Bois et al. 1995). Thus, through the binding of one or more hydroxyl groups to the substrate, a pro-carcinogenic substance may become carcinoogenic, as what occurs when benzopyrene is converted into benzopyrene-diol epoxide, a highly reactive compound (Bois et al. 1995). The reactions in phase II involve conjugation with an endogenous substrate (glutathione, sulfate, glucose, and acetate) via glutathione-S-transferases (GST), UDP-glucoronyltransferases, and N-acetyltransferases (NATs), which inactivate phase I metabolites, transforming them into more hydrophilic molecules suitable for excretion (Kroemer & Eichelbaum 1995). Therefore, the regulation and expression of enzymes of phases I and II, as well as their metabolic balance in the cell, may be important in determining the susceptibility to diseases related to exposure to toxic agents (Vineis 2002). Figure 4 explains the function of these enzymes.

Our group has consistently been investigating the influence of polymorphisms and genetic alterations in phases I and II enzymes in DTC susceptibility. Morari et al. (2002) studied 116 (49 benign thyroid lesions, 50 PTC, and 17 FTC) patients with thyroid disease and 300 healthy individuals and showed that the absence of both GSTT1 and GSTM1 genes was more frequent in DTC patients (12%) than in controls (5%) (P<0.05), increasing the risk of DTC 2.6 times. In 2004, Granja and colleagues studied another member of the GST family. An amino acid substitution (I105V) in the GSTP1 gene produces a variant enzyme with lower activity and less capability for detoxification of carcinogens than the WT. The authors compared the polymorphisms of 98 malignant nodules (77 PTC and 21 FTC) with 44 benign nodules and 157 healthy individuals. They showed that the inheritance of the polymorphism increased PTC susceptibility in more than seven times and FTC susceptibility in almost ten times (Granja et al. 2004b). In the same series of cases, Granja and colleagues did not find any association of GSTO1 (another member of the GSTs) with DTC susceptibility (Granja et al. 2005). Results from a North American study carried out in 201 patients with DTC, 103 patients with benign thyroid tumors, and 680 controls also indicated that the combined presence of GSTM1- and GSTT1-null genotypes increases DTC susceptibility (Ho et al. 2006).

Gaspar et al. (2004) observed that polymorphisms of GSTM1, GSTT1, and GSTP1 are risk factors for DTC in the Portuguese population, increasing the risk of developing the disease. However, these results were neither observed in the Spanish population (Hernandez et al. 2003) nor in the Polish population, probably, due to the low number of individuals included (Marciniak et al. 2006). Similarly, Li et al. (2012) studied three polymorphisms of GST (M1, T1, and P1) with DTC risk in 1819 cases and 3189 controls (14 abstracts), and concluded that these polymorphisms were not associated with DTC susceptibility.

Our group has also studied the influence of genes that encode CYP and NAT enzymes on DTC risk. Bufalo et al. (2006) studied 277 healthy individuals and 80 cases of benign thyroid lesions, as well as 168 cases of malignant thyroid tumors (136 PTC and 32 FTC), and demonstrated an inverse association of the polymorphism of CYP1A1 m1 and DTC, especially for PTC. Guilhen and colleagues studied the correlation of the polymorphisms of NAT2 with DTC susceptibility. They showed that the presence of 12A and the absence of 12B, 13, 14B, 14D, 6A, and 7A NAT2 haplotypes were risk factors for DTC. The inheritance of the rapid acetylation phenotype also doubled the risk for PTC (Guilhen et al. 2009).

In another study, our group also demonstrated that NAT2 increases susceptibility to sporadic medullary thyroid carcinoma (Barbieri et al. 2012), and that CYP1A2*F, GSTP1, and NAT2 might also play an important role in the risk for hereditary medullary thyroid carcinoma (Barbieri et al. 2013).

The study of polymorphisms in these enzymes could help with determining the levels of specific chemotherapy drugs for resistant DTCs, similarly to what is being done with vandetanib for MTC (2012) and tamoxifen for breast cancer (Hoskins et al. 2009). In addition, identifying a risk profile for thyroid diseases may help to delineate polygenic models of susceptibility and prognosis. Such models are particularly interesting, considering the elevated prevalence of thyroid diseases in the population, and may be helpful in selecting individuals for specific preventive interventions and for determining which patients are most likely to benefit from specific measures.

**Viruses**

Viruses are responsible for almost 20% of all human malignancies, but their carcinogenic mechanisms vary
depending on particular virus, target cells, and host factors involved (Stewart & Kleihues 2003, Avanzi et al. 2013). There is evidence that some viruses may change a normal cell into a neoplastic cell by interfering with the regular lifecycle of the cell, affecting cells that have already accumulated a number of genetic mutations (Avanzi et al. 2013, Fuentes-Gonzalez et al. 2013). Furthermore, viral proteins have already been associated with the modulation of several biological processes, including proliferation, differentiation, and apoptosis (Avanzi et al. 2013, Fuentes-Gonzalez et al. 2013). Other viruses not only seem to induce cell proliferation by the activation of MAPK and PI3K pathways, but also inhibit cell-cycle control through the inhibition of key proteins such as p53 and ATM (Noch & Khalili 2012). These viruses can also increase the oxidative stress on the cell and, by that means, interfere with cell metabolism, inducing the expression of factors such as HIFa and AMPK (Noch & Khalili 2012; Fig. 5).

Herpes viruses have the ability to cause a latent and persistent infection of the host cell that lasts for its lifetime (Avanzi et al. 2013). These viruses are involved with human malignancies and with autoimmune thyroid diseases. Our group showed that human herpes virus type 7 (HHV7) sequence was inserted into the DNA of peripheral blood cells of patients with GD. The presence of HHV7 was more frequent in GD patients than in healthy controls ($P<0.0001$), and the inheritance of the Pro/Pro 72TP53 variant seemed to favor HHV7 infection (OR = 2.835, $P = 0.02$), leading us to believe that HHV7, in concomitance with Pro/Pro 72TP53, triggers an autoimmune process that leads to GD (Leite 2010).

There is still little evidence of the association of DTC with herpes viruses. In a study by Jensen et al. (2010), DNAs of herpes simplex virus type 1 (HSV1) and HSV2 were found in 43/109 (39.4%) thyroid tumors and were associated with the overexpression of Nectin-1, a receptor of HSV that increases the susceptibility to HSV infection in thyroid cells. In addition, the presence of HSV2 DNA in these samples was more frequent in malignant than in benign thyroid tumors. Our group’s newest preliminary findings indicate that Epstein-Barr Virus (EBV) may be associated with thyroid tumors. In fact, we found a high viral load in thyroid tissues, especially in PTCs (Almeida et al. 2013). Although there is little evidence of a relationship between EBV and DTC, this virus has already been strongly associated with other human malignancies such as nasopharyngeal cancer, Burkitt’s lymphoma, and breast cancer (Raab-Traub 2002, Mazoumi et al. 2011, Grywalska et al. 2013, Kelly et al. 2013, Smith 2013). In DTC, EBV was previously investigated by Tsai et al. (2005) in 32 thyroid tissue samples, in a study including other types of viruses, with conventional PCR results not showing any evidence of its presence in the tumors investigated. In the same study, the only herpes virus found in thyroid tumors was cytomegalovirus in 4/32
(12.5%) positive cases (Tsai et al. 2005). These authors did not present any evidence of an interaction between the viruses and disease progression. Although we have evidence of the presence of herpes viruses in thyroid tissues, indicating some role of these viruses in thyroid malignancy, it remains unclear what their roles are in these cells and functional and long-term follow-up studies are necessary to characterize the interaction of these viruses and thyroid cells.

Another virus has also been associated with thyroid diseases: simian virus 40 (SV40) that came from Asian rhesus monkeys and has similarities with human polyomaviruses (Ozdarendeli et al. 2004). The oncogenicity of this virus is associated with the expression of T antigen (Tag), which interferes on the stability and integrity of the host cell and inhibits growth suppressor proteins such as p53 (Pipas 1992, Ludlow 1993, Ozdarendeli et al. 2004). This virus has been associated with several types of tumors including lymphomas, bone tumors, malignant mesothelioma, etc. (David et al. 2001, Jasani & Butel 2013, Cleaver et al. 2014). A few studies also reported the presence of DNA sequences of SV40 in DTC. Ozdarendeli et al. (2004) found four samples positive for SV40 out of 99 studied thyroid tissues. Vivaldi et al. (2003) found SV40 DNA sequences in thyroid tumors, normal thyroid tissues, and GD thyroid specimens and also in PBMC from healthy donors, and proposed that PBMC infection may lead the virus to different host tissues, causing different diseases.

Certainly, if we look for viruses in different kinds of human biological samples, they will be found, because we are exposed to them every day, everywhere. Nevertheless, it is necessary to better investigate the mechanisms of infection of all these viruses to understand how they can, in fact, cause or influence the development of human malignances, as well thyroid cancer.

**Summary/conclusions**

Although many authors have related the increasing incidence of DTC to an increase in access to health systems worldwide, there are other newly described factors that should not be dismissed, such as radiation exposure, iodine intake, and compounds with carcinogenic potential, such as a large class of xenobiotics to which we are exposed both by food ingestion and proximity to contaminated areas. These factors, which have increased in recent decades may be important for clinicians, helping to define preventive strategies and, ultimately, control the increasing incidence of DTCs.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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