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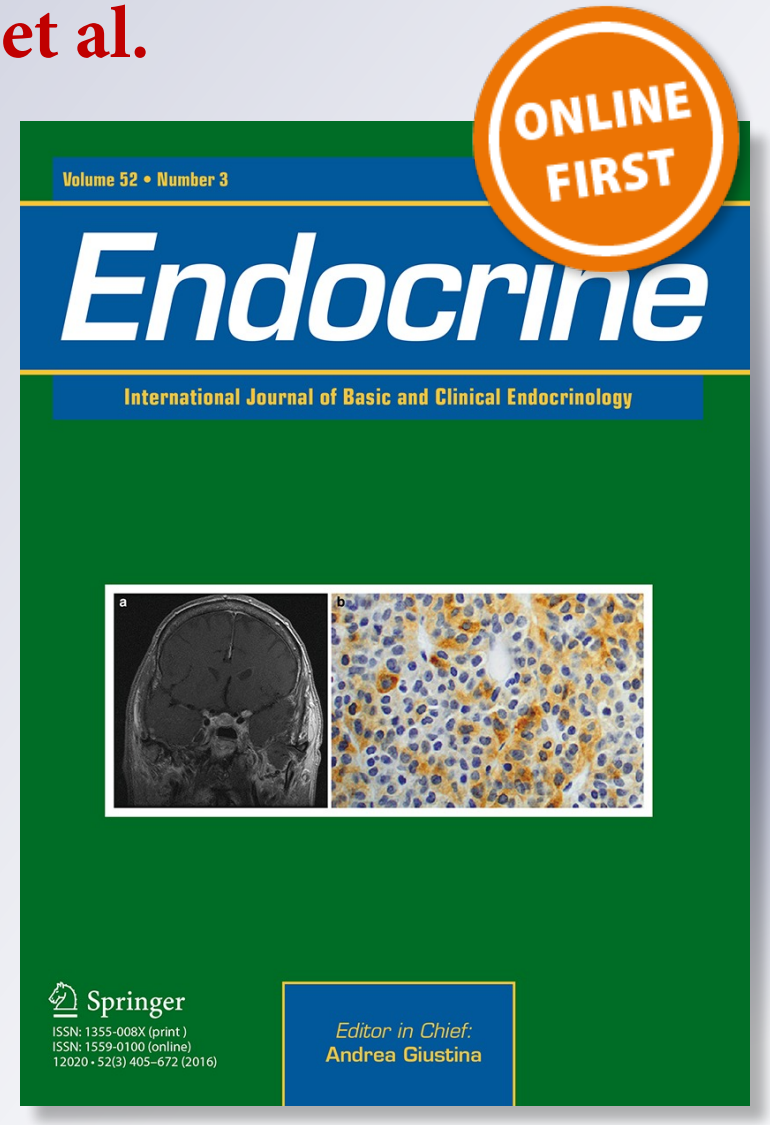
Endocrine
International Journal of Basic and Clinical Endocrinology

ISSN 1355-008X

Endocrine
DOI 10.1007/s12020-016-0992-8



Springer

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ORIGINAL ARTICLE

How do etiological factors can explain the different clinical features of patients with differentiated thyroid cancer and their histopathological findings?

Loredana Pagano[1] · Chiara Mele[1] · Debora Arpaia[2] · Maria Teresa Samà[1] · Marina Caputo[1] · Serena Ippolito[2] · Carmela Peirce[2] · Flavia Prodam[3] · Guido Valente[1] · Giuseppe Ciancia[4] · Gianluca Aimaretti[1] · Bernadette Biondi[2]

Received: 26 February 2016 / Accepted: 17 May 2016

Abstract The aim was to retrospectively analyse the clinical–histopathological characteristics of patients with newly diagnosis of differentiated thyroid cancer (DTC) referred to two Italian centres, one in Northern and the other in Southern Italy, between 2000 and 2013. 1081 patients were included and subdivided into two groups: group A (474 patients from Novara) and group B (607 patients from Naples). The group A came from the industrial area of Novara, while the Group B came from the areas around Vesuvius and Campi Flegrei. The two groups were comparable for iodine levels, body mass index, diagnostic timing and clinical procedures. For all patients, demographic and clinical data were collected. No difference was found in gender, whereas the age at diagnosis was later in the group A (group A 53.1 ± 15.16 years, group B 41.9 ± 14.25 years, $p < 0.001$). In both groups, the most frequent histotype was papillary thyroid cancer (PTC) with prevalence of follicular variant in group A ($p < 0.0001$) and classical variant in group B ($p < 0.0001$). Aggressive histological features were mainly seen in group A (bilaterality $p < 0.0001$, multifocality $p < 0.0001$ and thyroid capsular invasion $p < 0.0001$). Microcarcinomas were more frequent in group A ($p < 0.0001$) but mostly characterized by bilaterality ($p < 0.001$) and multifocality ($p < 0.04$). In both groups, tumour-associated thyroiditis showed a significant increase over the years (group A $p < 0.05$, group B $p < 0.04$). Environmental factors could justify the differences found in our study. These preliminary data should stimulate the need for an Italian Cancer Registry of DTC in order to allow an epidemiological characterization, allowing the identification of specific etiological factors and an improvement in the management of the disease.

Keywords Thyroid cancer · Tumourigenesis induction · Clinical–histopathological features · Environmental factors

Introduction

The incidence of the differentiated thyroid carcinoma (DTC) has been increasing in many countries over the last 30 years [1–11].

The most recent data about this massive increase in the incidence come from the U.S. SEER (Surveillance, Epidemiology, and End Results) which shows that the age-adjusted incidence rate has increased from 4.85/100,000/year in 1975 to 14.93/100,000/year in 2011 [1].

In Italy, a marked increase occurred over the last three decades, both in men (+9.1 % per year) and in women (+8.7 % per year), according to AIRTUM (Italian Association of Cancer Registries), AIOM data (Italian Association of Medical Oncology) and literature [11]; in particular, more than 16,000 new cases were seen in 2013 (4100 men and 12,200 women), representing about 4.5 % of all new cases [12].

The reported incidence increase in all countries is almost exclusively due to an increase in the papillary

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Published online: 26 May 2016

thyroid carcinomas variant (PTC), with no significant changes in the follicular (FTC), medullary and anaplastic form [2]. Despite the most part of PTC consists in indolent micro/small carcinomas [2], the mortality rate has not decreased, standing around 0.5 per 100,000 per year in both sexes in almost all countries [13, 14].

Therefore, even if the increased incidence could be attributed to a better diagnostic accuracy [11, 15, 16], we cannot exclude environmental and lifestyle causative factors [17–19].

Major data about epidemiology and risk factors for DTC come from geographical areas, such as United States, where the vastness, the presence of different ethnic groups and different lifestyles make difficult to evaluate the environmental carcinogens [2, 4–6]. In Italy, this limit could be avoided thanks to the territorial limited extension, the more homogeneous population and the comparable lifestyle in all regions [20–23].

The aim of our study was to retrospectively analyse the clinical and histopathological characteristics of Italian caucasic patients with DTC referred to two Italian centres, the University Hospital (AOU) "Maggiore della Carità" in Novara, in Northern Italy and the University Hospital (AOU), Federico II in Naples, in Southern Italy, in order to evaluate the possible differences of DTC in these populations compared to data reported in the national literature.

Patients and methods

We retrospectively analysed clinical and pathological features of patients with newly diagnosis of DTC referred to 2 clinical centres: "Maggiore della Carità" University Hospital (Novara) in Northern Italy and "Federico II" University Hospital (Naples) in Southern Italy, from January 2000 to December 2013. All cases were collected from the Pathology archive of each centre.

Patients were subdivided into two groups, according to the centre of origin (Group A = Novara; Group B = Naples).

The group A patients came from the eastern province of Novara, a typical industrial area, while the Group B population came from the areas around the volcano Vesuvius and Campi Flegrei, an active sunken volcanic area.

According to ARPA (Regional Agency for Environmental Protection) data, there are some differences in exposure between these two Italian regions: Novara population is exposed to industrial chemicals, such as formaldehyde and benzene [24], while Naples area is exposed to minerals of volcanic origin such as nitrates, vanadium, manganese and other heavy metals [25].

The two groups were comparable for iodine levels, body mass index (BMI), diagnostic timing and clinical procedures.

Patients data were collected through retrospective medical record review regarding demographics and clinical aspects (age, gender, BMI, ioduria, type of surgery) and histological reports including information about tumour size, extrathyroidal extension, multifocality, lymph-nodal (LN) metastasis and presence of peritumoural thyroiditis.

Environmental and occupational exposures were identified through a direct interview for each patient. Smoking habits, hormonal and genetic factors were not investigated because the evaluation of this clinical outcome was not a purpose of the study.

Patients with history of medical irradiation, poorly differentiated, anaplastic, medullary thyroid carcinomas and secondary tumours or living for less than 5 years in the analysed areas were excluded.

Our data relating to ioduria were extrapolated from a new document, which contains information about ioduria in 16 Italian regions including Piedmont and Campania. This document was published by Italian "Istituto Superiore di Sanità" in 2014 [26].

Histological diagnoses were blindly determined by two independent pathologists, specialized in thyroid pathology, belonging to the two centres. Pathologic staging was redefined according to the Tumour, Lymph Node, and Metastasis classification system based on the 6th edition of the UICC/AJCC TNM classification [27].

Moreover, we evaluated the frequency and histopathological characteristics of microcarcinomas (defined as tumours 1 cm or less in size [28]) in both the groups.

For all cases, tumour-associated thyroiditis was assessed. The histological criteria used to make this diagnosis included diffuse lymphoplasmacytic infiltration, germinal centres and enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (Hurthle cells), which are specific for Hashimoto's thyroiditis (HT) and also polynuclear macrophage-like and fibroblastic-like population specific for non-specific lymphocytic thyroiditis, which might represent perineoplastic inflammation, when occurring immediately adjacent to a tumour [29].

The results were expressed as mean ± standard deviation (SD) or percentage with 95 % confidence intervals.

The association between factors was assessed with the multinomial logistic regression for dichotomous or categorical variables. Continuous variables were analysed using student *t* test.

P values less than 0.05 were considered significant. The analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, Ill., USA).

Results

1081 patients were included in this study: group A = 474 patients and group B = 607 patients.

The clinical and histopathological characteristics of all patients are reported in Table 1.

Group A (474 cases)

In this population, the majority of patients were female (76.4 %) with a M:F ratio of 1:3. The mean age at diagnosis (mean ± SD) was 53.1 ± 15.16 years (range: 13.0–88.0 years); in particular, 68.6 % was aged

Table 1 Clinical and histopathological characteristics of all patients divided into two study groups: group A (Novara) and group B (Naples)

		GROUP A (NOVARA) (474 CASES)	GROUP B (NAPLES) (607 CASES)
Age at diagnosis	<45 years (%)	31.4	58.3
	≥45 years (%)	68.6	41.7
	Mean ± SD (years)	53.1 ± 15.16	41.9 ± 14.28
Gender	Male (%)	23.6	22.2
	Female (%)	76.4	77.8
Body Mass Index	Mean ± SD (Kg/m^2)	26.6 ± 4.52	27.1 ± 5.57
Type of surgery	Total or near total thyroidectomy (%)	99.2	99.7
	Lobectomy (%)	0.8	0.3
Lymphadenectomy	No (%)	71.9	53.1
	Yes (%)	28.1	46.9
Histotype	PTC (%)	90.0	89.0
	FTC (%)	9.0	11.0
	PTC + FTC (%)	1.0	0.0
PTC variant	Classic (%)	36.9	63.8
	Follicular (%)	37.3	19.9
	Classic and Follicular (%)	9.1	7.6
	Other (%)	16.7	8.7
Size	<1.0 cm (%)	44.1	30.4
	2.0 cm (%)	27.8	43.9
	2.0–4.0 cm (%)	22.6	21.9
	>4.0 cm (%)	5.5	3.8
Multifocality	Absent (%)	68.8	78.9
	Present (%)	31.2	21.1
Bilaterality	Absent (%)	74.7	86.8
	Present (%)	25.3	13.2
Capsular Invasion	Absent (%)	80.8	91.3
	Present (%)	19.2	8.7
Staging	Stage I (%)	75.3	88.4
(TNM 2010)	Stage II (%)	8.9	5.5
	Stage III (%)	11.4	4.1
	Stage IV (%)	4.4	2.0
Histological associated thyroiditis	Absent (%)	75.5	70.3
	Present (%)	24.5	29.7
Lymph Node Metastasis	Absent (%)	49.2	49.8
	Present (%)	50.8	50.2
TPOAb[a]	Absent (%)	70.0	67.0
	Present (%)	30.0	33.0

[a] TPOAb assays has a functional sensitivity of 25.0 U/mL and the analysis was automatically performed using "ADVIA Centaur ATPO" (Siemens Healthcare Diagnostic inc., Tarrytown, NY, USA)

>45 years. The mean BMI (mean ± SD) was 26.6 ± 4.52 kg/m^2.

Total thyroidectomy was performed in 99.2 % of cases and 28.1 % of patients also underwent lymphadenectomy.

The most frequent histotype was PTC (90.0 %), and the most widespread variant was the follicular one (37.3 % of all PTCs), followed by the classical variant (36.9 %). FTC was detected in 9.0 % of cases. Only 5.5 % of tumours were sized >4.0 cm, while microcarcinomas represented the majority of cases (44.1 %).

The 75.3 % of tumours were classified as stage I, followed by stage III tumours (11.4 %), with high frequency of thyroid capsular invasion (19.2 %). Tumours were bilateral in the 25.3 % of cases and multifocal in the 31.2 % of cases. Among patients who underwent lymphadenectomy, 50.8 % had lymph node metastasis.

Finally, tumour-associated thyroiditis was histologically found in 24.5 % of cases.

Group B (607 cases)

In this group, the disease was more frequent in females with M:F ratio of 1:3.

The mean age at diagnosis (mean ± SD) was 41.9 ± 14.28 years (range: 8.0-84.0 years); in particular, 58.3 % of the patients were aged <45 years. The mean BMI (mean ± SD) was 27.1 ± 5.57 kg/m^2.

99.7 % of patients underwent total thyroidectomy with lymphadenectomy in 46.9 % of cases.

The most frequent histotype was PTC (89.0 %), and the most widespread variant was the classical (63.8 % of total PTCs), followed by follicular (19.9 %). The 11.0 % of patients was affected by FTC.

Tumours sized >1.0 cm and <2.0 cm represented the majority of cases (43.9 % of cases).

Stage I tumours represented more than three-quarters of the cases (88.4 %), followed by stage II (5.5 %), stage III (4.1 %) and stage IV (2.0 %) tumours.

Tumours were bilateral in 13.2 % of cases and multifocal in 21.1 % of cases, and the thyroid capsular invasion was found only in 8.7 % of cases. Among patients who underwent lymphadenectomy, 50.2 % had lymph node metastasis.

Finally, the tumour-associated thyroiditis was histologically found in 29.7 % of cases.

Group A vs Group B

With regard to the clinical characteristics, the age at diagnosis was earlier in group B than in group A ($p < 0.001$) (Fig. 1).

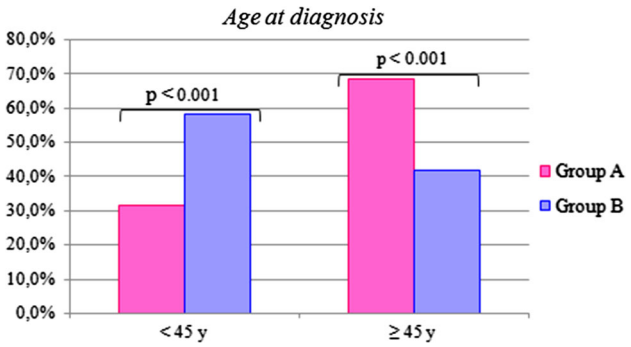

Fig. 1 Age at diagnosis in groups A and B

Moreover, no significant difference was found in BMI (26.6 ± 4.52 kg/m^2 in group A and 27.1 ± 5.57 kg/m^2 in group B).

In both populations, we observed an upward trend over time of PTC cases (Fig. 2).

Regarding histotype, the most frequent was PTC in both the groups; the follicular variant was more represented in group A, while the classical variant in group B ($p < 0.0001$) (Fig. 3). Furthermore, most aggressive variants were observed more in group A than in group B, although without statistical significance. Histopathological differences were found between the two populations: bilaterality (group A vs. group B, 25.3 % vs. 13.2 %, $p < 0.0001$), multifocality (group A vs. group B, 31.2 % vs. 21.1 %, $p < 0.0001$) and thyroid capsular invasion (group A vs. group B, 19.2 % vs. 8.7 %, $p < 0.0001$) (Fig. 4).

Regarding smaller tumours, microcarcinomas were significantly more frequent in group A ($p < 0.0001$) with respect to group B, and, similarly to macroscopic tumours, in Novara's group they were mostly characterized by bilaterality (group A vs. group B, 20.5 % vs. 8.3 %, $p < 0.001$), multifocality (group A vs. group B, 25.9 % vs. 16.6 %, $p < 0.04$) and, without reaching significance,

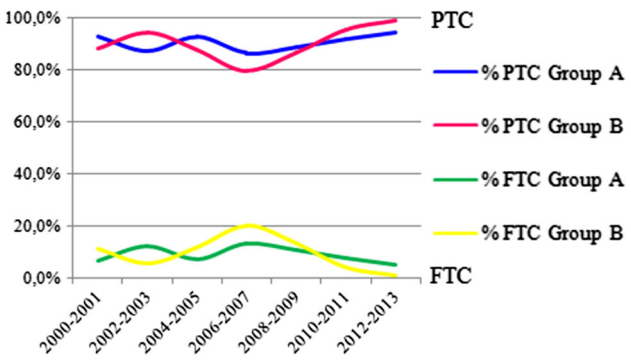

Fig. 2 PTC and FTC in groups A and B: trend over the years

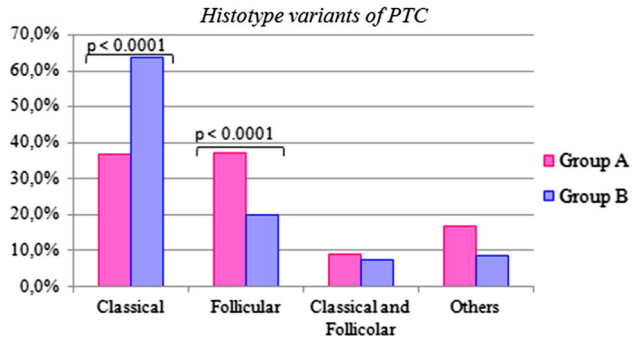

Fig. 3 Histotype variants of PTC in groups A and B

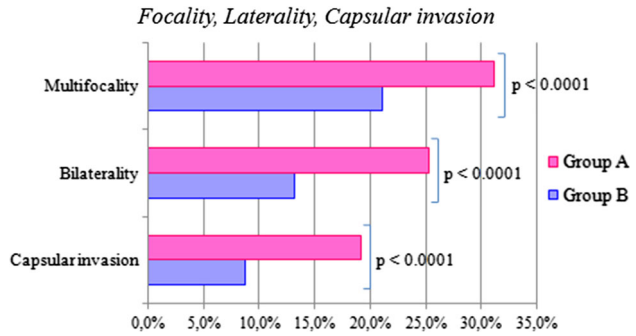

Fig. 4 Focality, laterality and thyroid capsular invasion in groups A and B

thyroid capsular invasion (group A vs. group B, 6.3 % vs. 4.1 %).

Therefore, stage I tumours were more represented in group B than in group A ($p < 0.0001$), considering the earliest age of discovery of the disease (Fig. 5).

With regard to the presence of lymph node metastasis (N) and distance metastasis (M) at the time of diagnosis, no difference was found between the two groups, nor about the presence of thyroiditis, considering both thyroid peroxidase antibodies (TPOAb) positivity and the presence of lymphocytic and non-specific lymphocytic peritumoral inflammation; however, this tumour-associated thyroiditis showed a significant progressive increase over the years, in both the populations ($p < 0.05$ in group A, $p < 0.04$ in group B) (Fig. 6).

Discussion

The study of clinical, histopathological and epidemiological characteristics directly influences diagnostic and therapeutic decisions in the field of oncology [30].

In recent years, the literature reported a significant increase in the incidence of PTC worldwide and in particular in Italy [1–11].

In our study, we observed the same upward trend in incidence of thyroid cancer cases in both the cohorts studied; however, considering the clinical and histopathological characteristics at the time of diagnosis, some differences emerge, leading to hypothesize that environmental and carcinogens factors could change the DTC tumourigenesis.

First, we observed a difference in age at diagnosis between the two populations. In fact, in the Neapolitan population, thyroid cancer seems to be diagnosed earlier than in Novara population, in agreement with other national and international studies reported in literature [11, 31]. Interestingly, in group B, we observed a high percentage of subjects younger than 25 years. This anticipation in the age at diagnosis was also found in the Italian study by Malandrino and co-workers [20] involving populations living in volcanic areas. As a matter of fact, Neapolitan patients mainly came from the areas around the volcano Vesuvius and Campi Flegrei, which are exposed to volcanic minerals, according to ARPA data [25]. Therefore, this phenomenon of age anticipation could be related to the exposure to one or more volcanic carcinogens (in particular heavy metals) [21–23, 32–36]. It has already been reported that high heavy metal concentration in the soil or water would act as endocrine disruptors, increasing the risk for thyroid cancer in younger age because their

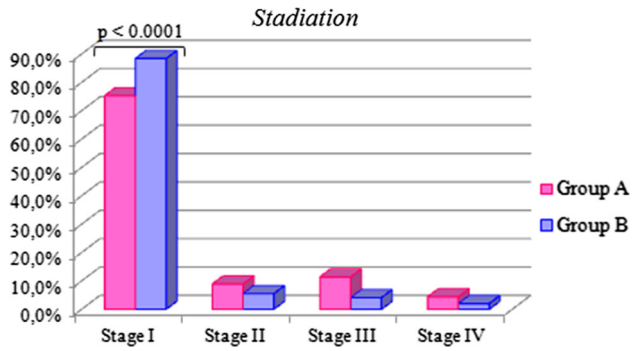

Fig. 5 Staging in groups A and B

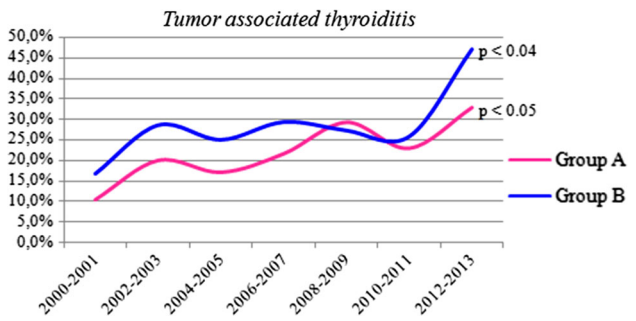

Fig. 6 Tumour-associated thyroiditis in groups A and B: trend over the years

effects may manifest in utero, in children and in adulthood [37]. Moreover, considering only thyroid cancers larger than 1.0 cm, in this group, we found a significantly higher incidence of larger thyroid cancers, even papillary types, according to other studies regarding populations living in volcanic areas [21, 36]. In these areas, there seems to be a significant inverse relationship between tumour size and age at diagnosis (the mean tumour size was significantly higher in younger patients in a Sicilian cohort around Etna volcano) [38].

On the other hand, in Novara's group, we found older age at diagnosis, differently from what reported in literature [2, 11, 31]. It has to be considered that also Fugazzola and co-workers (*Abstract no. 20. Abstract book from 9° Congresso Associazione Italiana della Tiroide*) recently showed an increased age at diagnosis in their population living in Milan and surrounding areas, close to Novara region.

This increase in thyroid cancer incidence in elderly population could be due to the combined effect of radiations and natural changing of hormonal status in this age [39, 40]. Therefore, considering that Northern Italy was more exposed to Chernobyl's nuclear radiations than Southern Italy, as shown in the European map from *Chernobyl, 22 years later, CBS News* [41], we could speculate that in Novara's group, we are now observing the second peak of tumours after about 20 years of latency.

Another interesting observation coming from our data concerns the histopathological features. In Novara's group, we found a higher percentage of follicular variant of PTC (FVPTC) compared to Neapolitan group and other Italian cohorts [42]. The FVPTC is a heterogeneous disease that includes two different groups of tumours: one similar to the classical PTC in its behaviour and another more similar to FTC in its invasive features and molecular profile [43]. Certainly, the re-classification of FVPTC in these 2 subgroups and the genetic characterization of tumours in our population might be helpful to explain their higher incidence in Novara's group.

Furthermore, in Novara's cohort, CDT showed more histopathological aggressive features already at diagnosis, such as thyroid capsular invasion, bilaterality and multifocality. The same was seen in microcarcinomas, especially with regard to bilaterality and multifocality, even if in literature these two characteristics do not seem to adversely affect survival [11]. This result corroborates the data available in the literature [44] showing that microscopic thyroid cancer at presentation can be as aggressive as macroscopic disease, regardless of whether the tumour is incidentally discovered or not. Molecular studies would be able to differentiate, at an early stage, microcarcinomas with an aggressive behaviour from microcarcinomas with an indolent clinical course. The increased aggressiveness could correlate with and another risk factor, of which Novara's population is exposed, chemical pollutants in atmosphere [45, 46]. As a matter of fact, Novara is placed in a predominantly industrial area and the population is exposed to chemical pollutants such as formaldehyde and benzene [24]. Most of the population came from the Eastern part of the Novara province, where the industries are predominantly placed, especially in the textile and engineering fields; about 30.0 % of our patients were employed in the textile sector and about 25.0 % in the engineering industry. According to ARPA data collected from 2003 to 2009 [24], environmental exposure to formaldehyde and benzene in this area was recognized to be higher than in the rest of Italy. The correlation between thyroid cancer and exposure to formaldehyde and benzene emerges in several studies reported in literature [47–49]. In particular, a study conducted on a cohort of Chinese women working in the textile industry in Shanghai showed a strong association between thyroid cancer and exposure to formaldehyde [47]. Even exposure to benzene has been shown to be related to thyroid cancer, but with a lower extent than formaldehyde. To date, few studies focused on the role of these substances in thyroid cancer and on the mechanisms of inducing tumourigenesis, but all agree with the hypothesis that these chemicals can determine both the tumour onset and its more aggressive behaviour [47–49].

We can speculate that in the Northern area both environmental factors (radiation or chemical pollutants exposure), together or alone might play a role in thyroid tumourigenesis. From a recent review by Marcello and coworkers [23], radiation exposure seems to be the cause of a high percentage of RET/PTC rearrangements, while chemical pollutants seem to be associated with BRAF mutations, and more specifically $BRAF^{V600E}$ point mutation. Thus, the study of the underlying biological and molecular pathways in our population could help us to understand which etiopathogenetic hypothesis is most probable.

Finally, no significant difference was found in iodine level, being median urinary iodine 87 μg/L in Naples [50] and 98 μg/L in Piedmont [26], as both populations belong to region with mild iodine deficiency. In both the groups, we found a similar distribution of associated thyroiditis with an increasing trend over time in term of both tumour-associated inflammation and TPOAb positivity. This could be explained by 2 hypothesis: 1) the increase in the iodine intake [51] as a result of programmes of iodine prophylaxis [52]; 2) external factors (still unknown) probably triggering both thyroid disorders, inflammation and tumour [53]. However, if the increased frequency of thyroiditis would be an additional factor contributing to the continuous increase in incidence of thyroid cancer, it is still debated [54, 55].

The present study has some potential limitations. It was retrospective and cases were collected from the Pathology archives, so we cannot supply complete information about the reasons of all the thyroid surgical interventions and about the incidental nature of all microcarcinomas. Moreover, we do not have a control group, and thus, we compared our data with others coming only from Italian studies.

The role of these potential chemicals and environmental factors in inducing thyroid cancer is only conceivable. A greater number of studies are required to classify the role of these substances, in order to accurately understand their physiopathological mechanisms of induction of tumourigenesis and the clinical and histopathological characteristics, they are responsible for.

Conclusions

The more sensitive and widespread diagnostic procedures can only partially justify the progressive increase in DTC.

More studies are necessary to investigate the role of environmental factors, which include both volcanic elements and industrial chemical pollutants.

In this scenario, a national cancer registry could be a mirror of the different territories and could provide a better understanding of the different risk factors and mechanisms involved in tumourigenesis.

It could also allow to carry out comparative studies, through which it would be possible to outline the characteristics of the populations at risk and then to perform screening programmes and prevention, improving the management of DTC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

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