Environmental, Lifestyle, and Anthropometric Risk Factors for Differentiated Thyroid Cancer in Cuba: A Case-Control Study

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Abstract

Background: The incidence of differentiated thyroid carcinoma (DTC) is low in people of African origin and higher in populations living on islands, but there is no well-established explanation for these differences. Cuba is a multiethnic nation with people of African and Spanish descent. Until now, no study on the risk factors of DTC has focused on the Cuban population. Our aim is to establish the role of environmental and lifestyle factors and to relate anthropometric measurements to the risk of developing DTC in Cuba. **Methods:** We performed a case-control study of 203 DTC patients treated in two hospitals in Havana and 212 controls living in the area covered by these hospitals (i.e. parts of Havana and the municipality of Jaruco). Risk factors were analyzed using conditional logistic regression. **Results:** As has been shown by other studies, we found that non-African ethnicity, never smoking, parity, and high body mass index are risk factors significantly associated with DTC, whereas a history of exposure to ionizing radiation and level of education were not significantly related with disease development. Being rhesus factor-positive, having a personal history of benign thyroid disorder, agricultural occupation, and consumption of artesian well water were also associated with a significantly increased risk of developing DTC. **Conclusions:** The original findings reported here concern the risk of DTC that was associated with non-African ethnicity, positive rhesus factor, farming, and drinking water from an artesian well.

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Introduction

Registering the incidence of differentiated thyroid carcinoma (DTC) is highly dependent on the medical practice and, in particular, on organized or opportunistic screening [1]. Therefore, comparing reported incidences

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requires careful investigation. Despite these limitations, it is now well established that the incidence of DTC is lower in people of African ethnicity origin than in others [2]. For example, in Martinique, a French Antilles island where most of the population is of African origin, the world age-standardized rate (ASR) of incidence was 0.8/100,000 men and 3.3/100,000 women during 1981–2000 [3]. These values are at least three times lower than those reported in metropolitan France [4]. Within the United States, the incidence of DTC is lower in people of African origin than in those of other ethnicities [5].

Another characteristic of DTC is its high incidence in island populations [6, 7], particularly in volcanic regions of islands [8, 9]. In Sicily, for example, the world population ASR was 17.8/100,000 women and 3.7/100,000 men during 2002–2004 [8]. In the Pacific islands, the ASR of incidence is particularly elevated. For example, in French Polynesia it was 24.6/100,000 women and in New Caledonia it reached 71.4/100,000 Melanesian women during 1985–1999 [10].

Until now, there are no clear explanations for these incidence variations. The only well-established risk factors of developing thyroid cancer are radiation exposure, a family history of thyroid cancer, residing in an iodine-deficient area, reproductive history, and body size [11]. No effect of alcohol, coffee, or other food groups or nutrients on the risk of developing thyroid cancer have been established. Increased height and weight at diagnosis show a moderate positive association with the risk of thyroid cancer [12]. Cuba is the largest island in the Caribbean Sea with an estimated population of over 11 million people (5,571,647 males and 5,592,287 females) according to the 2002 Census [13] and has a mixed ethnic composition with a large proportion of people of African or Spanish descent. Before colonization by Spain, Cuba was occupied by Native Americans, who had migrated from the mainland of North, Central and South America, several centuries before [14]. According to the 2002 Census, Afro-Cubans accounted for 35% of the population [13]. Their ancestors originated predominantly from the Congo in Central Africa.

Thyroid cancer is the sixth most common cancer affecting females in Cuba. It is sixfold more frequent in females than males. In 2009, the ASR of incidence was around 4.1/100,000 women and 1.0/100,000 in men [15].

This study reports the results of the first etiological observational study on thyroid cancer in Cuba. Our goal was to establish the role of environmental and lifestyle factors and to relate anthropometric measurements to the risk of developing DTC in Cuba.

Materials and Methods

This case-control study was carried out in Havana, Cuba, and was revised and approved by the Clinical Research Ethics Committee of the National Institute of Oncology and Radiobiology (INOR), Havana, Cuba. Informed written consent was obtained from all of the participants in the study.

Subject Selection and Interviews
Patients aged between 17 and 60 years who were living in Havana and its surrounding municipality of Jaruco (30 km from Havana), and were treated for DTC between 2000 and 2011 at INOR and at the Institute of Endocrinology, were eligible for the study. Potential cases were selected from the National Cancer Registry databases (C73 ICD-10) and were cross-referenced with the INOR Pathology Register. On average, around 25–30 patients who fit these criteria were identified for each year of the study period. In order to achieve the estimated sample size, the selection was extended to include incident cases. Of the 240 eligible DTC cases, 37 (15%) individuals were not interviewed because they could not be located (n = 32) or refused to participate (n = 5). The final study population consisted of 203 cases. Time of the survey was either 0 or 1 for 37% of the cases, while 19% cases had a lag time >5.

Controls (229) were selected from the general population living in Havana city and its surrounding areas municipality of Jaruco using consultation files from primary care units (family doctors). They were frequency-matched with cases by age at cancer diagnosis of the cases (±5 years) and gender. Of the 229 potential controls, 17 refused and 212 agreed to be interviewed.

Both cases and controls were interviewed face-to-face by trained professionals (nursing and medical staff) using a structured questionnaire between January 2009 and December 2011. A standardized questionnaire was used to collect data on demographic characteristics (age, gender, place of residence, and occupation), blood group, rhesus factor status, anthropometric parameters, reproductive and hormonal history, lifestyle (smoking habits, alcohol consumption), exposure to radiation or chemicals, personal medical history and family medical history in first-degree relatives. Size, blood group and rhesus factor collected by interviewers were compared to those in the national identity card and in medical records for cases.

Interviewers were trained to collect information related to a year before diagnosis for cases and a year before interview for controls. The majority of interviews were conducted in the presence of a parent or relative. Some were conducted at the workplace in the presence of a general practitioner.

Parameters Analyzed
The study participants were classified into three categories according to the ethnicity of their parents: European (both parents of European origin), African (both parents of African origin) and Other (all other combinations of parental origin). Body mass index (BMI) was defined as weight (kg) divided by height (m) squared and body surface area (BSA) was calculated using the Boyd formula: BSA $(m^2) = 0.0003207 \times (weight)^{0.7285 - (0.0188 \times \log(weight))} \times (height)^{0.3}$, where weight is expressed in grams and height in centimeters [16]. Quantitative factors were categorized into tertiles based on their distribution among the controls. Anthropometric categorization was defined separately for men and women.

Statistical Analysis

Nineteen strata were defined based on age and gender, 7 for men and 12 for women (of whom there were more individuals). These numbers were chosen so that there was at least 1 case and 1 control in each class. Conditional logistic regression was performed using with SAS software version 9.3 (SAS Institute, Inc., Cary, N.C., USA). For each parameter studied, the crude odds ratio (OR) stratified on age and gender, and the adjusted OR, also adjusted for ethnic group, level of education, number of pregnancies, height (three categories for each gender) and BMI (three categories), and the corresponding 95% confidence interval (CI) were estimated. In this analysis, the results for subjects of both genders were combined, except for the analyses on reproductive and hormonal factors.

Assuming a prevalence of exposure close to 30%, the size of this study (about 200 cases and 200 controls) allowed us to reach a power of 80% for evidencing the role of a risk factor associated with an OR of 1.8 when accepting a type I error of 5%.

Results

Of the 203 cases (mean age at diagnosis 38.2 years, range 17–60), 88% were women. The characteristics of the cases are shown in table 1. Papillary carcinoma was the most frequent histological type (189 cases) and of these, 20 cases presented a mixed papillary follicular variant. Follicular carcinoma was less frequent (14 cases) and 1 of these cases presented an oncocytic variant. On average, papillary carcinomas were larger than follicular carcinomas, with a mean volume of 20.71 mm^3 for papillary carcinomas and 17.85 mm^3 for follicular carcinomas.

Table 2 shows the putative risk factors for thyroid cancer that our analyses are adjusted for. Being of African descent was associated with a twofold lower risk of DTC when compared to being of European descent (adjusted OR 0.4; 95% CI 0.2–0.8). The OR for smokers was 0.6 (95% CI 0.4–0.9) when compared to those who had never smoked. Meanwhile, parity and BMI were significantly associated with an increased risk for DTC. BMI in the range 25–30 was significantly associated with an increased risk of DTC when compared to normal weight. Additionally, a positive but not significant association with a BMI >30 was observed. In women, the risk of DTC was significantly associated to number of pregnancies. The OR increased from 2.5 for two pregnancies to 3.8 for three or more pregnancies when compared to nulliparous.

A significantly increased risk of developing DTC emerged for subjects that were rhesus factor-positive (adjusted OR 3.2; 95% CI 1.6–7.0), had a personal history of benign thyroid pathology, such as a goiter (adjusted OR 10.1; 95% CI 4.8–21.2), and had hyper-/hypothyroidism (adjusted OR 4.5; 95% CI 1.3–14.9). Similarly, an increased thyroid cancer risk was associated with subjects that had an agricultural occupation (adjusted OR 3.7; 95% CI 1.4–9.5), or water supplied by an artesian well (adjusted OR 4.4; 95% CI 2.0–9.7). A lower risk of DTC was found for those with blood group B (adjusted OR 0.4; 95% CI 0.2–0.9) when compared to blood type O. BSA, waist size, and alcohol consumption were not significantly associated with thyroid cancer (table 3).

Table 1. Characteristics of cases

	n	%
Gender		
Male	24	11.8
Female	179	88.2
Time between diagnosis and interview		
0–2 years	101	49.8
3–5 years	63	31.0
6–11 years	39	19.2
Year of diagnosis		
2000–2005	50	24.6
2006–2008	64	31.5
2009–2011	89	43.8
Age at diagnosis		
17–20	10	4.9
21–25	16	7.9
26–30	12	5.9
31–35	34	16.8
36–40	46	22.7
41–45	41	20.2
46–50	30	14.8
51–55	7	3.5
56–60	7	3.5
Histology		
Papillary	189	93.1
Follicular	14	6.9
Volume of the tumor		
Papillary		
microcarcinoma	4	2.0
<5 mm^3	4	2.0
5–10 mm^3	33	16.3
11–20 mm^3	85	41.9
21–40 mm^3	49	24.1
>40 mm^3	14	6.9
Follicular		
microcarcinoma	0	0.0
<5 mm^3	1	0.5
5–10 mm^3	2	1.0
11–20 mm^3	5	2.5
21–40 mm^3	6	3.0
>40 mm^3	0	0.0

Table 2. ORs and 95% CIs of known DTC risk factors

Variables	Cases (n = 203)	Controls (n = 212)	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Ethnic group				
Both parents European	57	38	1*	1*
Both parents African	49	75	0.4 (0.3–0.8)	0.4 (0.2–0.8)
Other (mixed race)	97	99	0.6 (0.4–1.1)	0.7 (0.4–1.2)
Education level				
Secondary school level and below	23	18	1*	1*
High school	56	66	0.8 (0.4–1.6)	1.0 (0.4–2.1)
Pre-university	57	57	0.9 (0.4–1.9)	1.2 (0.5–2.5)
University	67	71	0.9 (0.4–1.8)	1.0 (0.4–1.2)
Height (m)				
Men <1.71; women <1.59	60	71	1*	1*
Men 1.71–≤1.78; women 1.59–≤1.65	74	66	1.3 (0.8–2.1)	1.37 (0.8–2.3)
Men >1.78; women >1.65	69	75	1.1 (0.7–1.7)	1.21 (0.7–2.0)
BMI				
<25	93	125	1*	1*
25–30	74	58	1.8 (1.1–2.8)	1.7 (1.1–2.8)
>30	36	29	1.8 (1.0–3.2)	1.7 (0.9–3.2)
Smoking status				
Never	144	125	1*	1*
Ever	59	87	0.6 (0.4–0.9)	0.6 (0.4–0.9)
Number of pregnancies (only for women)				
Nullipara	16	32	1*	1*
1	16	32	1.2 (0.5–2.8)	1.3 (0.5–3.4)
2	34	32	2.6 (1.1–5.9)	2.5 (1.1–6.1)
3 and more	113	77	3.7 (1.8–7.9)	3.8 (1.7–8.3)
Exposure to ionizing radiation[3]				
None	188	200	1*	1*
Radiotherapy	6	3	2.2 (0.5–9.1)	1.9 (0.4–9.8)
Head, neck, or thorax scanner[4]	4	2	2.3 (0.4–12.8)	2.4 (0.4–15.2)
Occupational exposure	5	7	0.8 (0.2–2.6)	0.7 (0.2–2.4)

[1] Stratified for gender and age classes. [2] Stratified for gender and age classes and adjusted for all the following factors: smoking status, ethnic group, level of education, number of pregnancies, height, and BMI, at the exception of the studied factor. [3] The numbers are the cases and controls for the 'yes' modality of each variable. [4] Excluding cases or controls treated by radiotherapy (n = 9). * Reference category.

Only 7 cases and 3 controls reported a history of thyroid cancer in a first-degree relative (OR 2.7; 95% CI 0.6–11.6). There was no significant difference in the build of the parents between cases and controls (table 4).

Among women, in addition to the known increased risk associated with parity (table 1), experiencing menarche before 12 years of age or after 14 or having had irregular menstrual cycles was also associated with a higher, though not statistically significant, risk of DTC (table 5). In this age-adjusted analysis, being postmenopausal was associated with an increased though not statistically significant risk of developing thyroid cancer.

Discussion

This case-control study is the first to focus on the risk factors for DTC in the Cuban population. Our novel findings reveal an association between the risk of developing thyroid cancer with non-African ethnicity, a positive rhesus factor, farming, and using water from an artesian well. In addition, this study confirms that the risk of developing DTC increases with increased parity and BMI, with a personal history of benign thyroid disease, and is higher in non-smokers than in smokers.

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Table 3. ORs and 95% CIs of DTC risk factors related to personal history and lifestyle characteristics

Variables	Cases (n = 203)	Controls (n = 212)	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Blood group (unknown n = 56)				
O	100	77	1*	1*
A	56	69	0.6 (0.4–1)	0.7 (0.4–1.1)
B	15	31	0.4 (0.2–0.8)	0.4 (0.2–0.9)
AB	7	4	1.2 (0.3–4.3)	3.1 (0.7–12.7)
Rhesus factor (unknown n = 55)				
Negative	13	36	1*	1*
Positive	166	145	3.2 (1.6–6.3)	3.4 (1.6–7.0)
BSA[3] (m^2)				
Men <1.90; women <1.60	43	63	1*	1*
Men 1.90–2.05; women 1.60–1.74	65	74	1.2 (0.7–2.1)	1.2 (0.7–2.1)
Men >2.05; women >1.74	95	75	1.7 (1.0–2.9)	1.5 (0.9–2.6)
Size of waist (cm)				
Men <76; women <74	72	110	1*	1*
Men 76–≤91; women 74–84	56	48	1.8 (1.1–3.0)	1.4 (0.8–2.5)
Men >91; women >84	75	54	2.2 (1.4–3.6)	1.4 (0.8–2.6)
Other thyroid disorders				
None	128	197	1*	1*
Goiter	65	10	8.8 (4.4–17.5)	10.1 (4.8–21.2)
Hyper-/hypothyroidism	10	5	3.6 (1.2-10.9)	4.5 (1.3-14.9)
Diabetes				
No	196	207	1*	1*
Yes	7	5	1.8 (0.5–6.2)	1.8 (0.5–7.1)
Living conditions				
Agricultural occupation				
No	182	205	1*	1*
Yes	21	7	4.0 (1.6–9.7)	3.7 (1.4–9.5)
Exposure to chemicals				
No	177	179	1*	1*
Yes	26	33	0.8 (0.5–1.5)	0.7 (0.4–1.3)
Water supply				
Only public water network	158	191	1*	1*
Fountain	4	3	1.6 (0.4–7.4)	1.3 (0.3–6.9)
Artesian well	40	9	5.2 (2.4–11.2)	4.3 (1.9–9.6)
Missing	1	9		
Alcohol consumption (glasses/week)				
0	167	130	1*	1*
1–5	29	64	0.3 (0.2–0.6)	0.3 (0.2–0.6)
≥6	7	18	0.4 (0.1–0.9)	0.4 (0.1–1.1)

[1] Stratified for gender and age classes. [2] Stratified for gender and age classes and adjusted for smoking status, ethnic group, level of education, number of pregnancies, height, and BMI. [3] Height and BMI are not included in adjustment variables for BSA. * Reference category.

Sample size may be the main limitation of this case-control study which limits its power and prevented the testing of the interactions between the risk factors, especially interactions with the ethnic origin of the subjects.

Although the geographical area was not included among matching variables, we tried to select controls from the same general geographic areas as the cases. This was possible because for each case selected from the National Cancer Registry databases (C73 ICD-10) and validated with the INOR Pathology Register, we were able to access the consultation file of the primary care units (family doctors) of the cases and select the control from this

Table 4. ORs and 95% CIs of DTC risk factors related to family history characteristics

Variables	Cases (n = 203)	Controls (n = 212)	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Family history of thyroid pathology				
None	165	177	1*	1*
Thyroid cancer	7	3	2.3 (0.6–9.2)	2.7 (0.6–12.0)
Goiter	16	19	0.9 (0.4–1.8)	1.1 (0.5–2.4)
Hyper-/hypothyroidism	15	13	1.3 (0.6-2.9)	1.5 (0.6-3.4)
Family history of other cancer				
No	164	165	1*	1*
Yes	39	47	0.8 (0.5–1.3)	0.8 (0.5–1.4)
Father's build (unknown n = 6)				
Thin	63	55	1*	1*
Normal	107	117	0.8 (0.5–1.3)	0.7 (0.5–1.2)
Large	30	37	0.7 (0.4–1.3)	0.7 (0.4–1.3)
Mother's build (unknown n = 4)				
Thin	44	43	1*	1*
Normal	124	124	1.0 (0.6–1.7)	1.1 (0.6–1.8)
Large	33	43	0.8 (0.4–1.5)	0.7 (0.4–1.4)

[1] Stratified for gender and age classes. [2] Stratified for gender and age classes and adjusted for smoking status, ethnical group, level of education, number of pregnancies, height, and BMI. * Reference category.

Table 5. ORs and 95% CIs of DTC risk factors related to selected hormonal and reproductive characteristics

Variables	Cases (n = 179)	Controls (n = 173)	Crude OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Age at menarche (unknown = 10)				
≤11	53	42	1.4 (0.9–2.4)	1.5 (0.9–2.7)
12–14	79	95	1*	1*
≥15	43	30	1.6 (0.9–2.9)	1.7 (0.9–3.0)
Irregular cycles (unknown = 15)				
No	140	140	1*	1*
Yes	33	24	1.4 (0.8–2.6)	1.6 (0.9–3.1)
Hormonal contraceptive				
No	89	91	1*	1*
Yes	90	82	1.1 (0.7–1.7)	1.0 (0.7–1.6)
Gestational diabetes				
No	172	168	1*	1*
Yes	7	5	1.4 (0.4–4.5)	1.4 (0.6–3.1)
Mammography				
No	161	157	1*	1*
Yes	18	16	1.1 (0.5–2.3)	1.1 (0.5–2.6)
Menopausal status (unknown = 9)				
Still menstruating	147	152	1*	1*
Natural	15	7	2.4 (0.8–7.0)	2.6 (0.8–8.2)
Artificial	14	8	1.8 (0.6–4.8)	1.4 (0.5–3.8)

[1] Stratified for gender and age classes. [2] Stratified for gender and age classes and adjusted for smoking status, ethnic group, level of education, number of pregnancies, height, and BMI. * Reference category.

file. The living places of cases and controls were theoretically the same – Havana and the surrounding municipality of Jaruco. In reality, it was probably not true because cases were selected only if treated at INOR or at the Institute of Endocrinology. These two hospitals probably do not cover all of Havana and therefore the cases and controls may not have belonged to the same population. We were not able to quantify this potential bias and its consequences.

In the multifactorial analyses, we adjusted for all suspected risks factors for thyroid cancer which were significant in the univariate analysis shown in table 2. We also adjusted for educational level because this variable was found to be a significant risk factor in many previous studies, and in order to indirectly adjust for unknown factors linked to educational level, but not collected in the questionnaire, as well as for differences in the areas of residence.

Although the frequency matching process in our study was based on the age at diagnosis of cases and while the at-risk period considered for interviews was specified to interviewers as ending 1 year before the diagnosis for cases and 1 year before the interviews were conducted for controls, these specifications may not been applied systematically. The effects of potential misapplications of these rules could not have been anticipated. Concerning anthropometric parameters, it should be noted that variation in weight within the few years after thyroid cancer diagnosis is probably low [17]. Although the weight was self-reported, the association between BMI and DTC might be biased due to a recall bias.

Of the cases, 19% were interviewed 6 years or more after cancer diagnosis, and these and their controls were asked about exposure during the period up to 1 year before diagnosis of cancers or corresponding period for controls. This long delay could have introduced a recall bias. This could explain our findings because when excluding these cases and their controls, our results remain largely similar.

Since the subjects were primarily selected from urban areas, our ability to test the effect of exposure to rural environments and associated factors such as the variability of water supplies on the risk for developing DTC was limited.

The inverse association between thyroid cancer and smoking has been suggested, mainly by case-control studies. Smoking has been associated with reduced serum levels of thyroid-stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4), a lower prevalence of serum thyroid autoantibodies, and a higher risk of Graves' hyperthyroidism. TSH, in particular, has long been hypothesized to play a major role in the development of thyroid cancer [17–20].

There were approximately twice as many controls of African origin as cases. Due to the nature of the Cuban medical system, it is unlikely that this is the result of the African population not having access to medical care. This finding is consistent with the low risk of developing thyroid cancer that has been observed in Martinique, where most of the population is of African origin [3]. This ratio of two is similar to that observed in the US Program of the Surveillance, Epidemiology and End Results (SEER) between populations of European and African origin [2].

We found a higher proportion of cases that were positive for rhesus factor than controls. To the best of our knowledge, the association between this factor and a risk of developing DTC has not been studied before.

While our findings on farming are in agreement with some results reported in an agricultural health study [21] and animal studies [22], until recently there has been relatively little data to support the association between specific exposure of farmers to certain pesticides and the risk of developing thyroid cancer. This could be because thyroid cancer is a rare cancer and has not been well studied even in recently initiated large cohort studies that focused on the agricultural population [23].

An interesting result of this study was determining the link between having an artesian well as a water supply and the risk of developing thyroid cancer. In a cohort study linking the incidence of cancer and exposure to fertilizer, Ward and colleagues [24, 25] also demonstrated an increased risk of developing thyroid cancer in subjects drinking water from an artesian well. They suggested that this result could be due to a higher concentration of nitrate which occurs in water from an artesian well as compared to water from the public water network. Another explanation could be the occurrence of metals or other elements in water from an artesian well. Indeed, the high incidence of thyroid cancer observed on the population of several islands, such as the French Polynesia archipelagos [10] or Sicily, has been associated with a high concentration of metals in drinking water [8]. If such elements are found in higher concentrations in artesian well water than in the public water network, these findings could explain our results.

This Cuban case-control study confirms that a higher number of pregnancies, a large BSA and a personal history of benign thyroid disease are associated with a high-

er risk of developing thyroid cancer, whereas smoking is associated with a lower risk. These thyroid cancer risk factors are now well established [11]. We did not observe a significantly increased risk associated with exposure to ionizing radiation, regardless of its origin (medical or occupational exposure). This may be because of the small number of cases included in our study.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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