DIETARY AND FEMALE REPRODUCTIVE RISK FACTORS FOR THYROID CANCER: A CASE-CONTROL STUDY IN WESTERN ALGERIA

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Abstract – Objective: Thyroid cancer is the most common endocrine malignancy with a higher incidence in women than men. This study aims to determine reproductive and dietary risk factors for thyroid cancer in women of Western region of Algeria.

Patients and Methods: Fifty-three patients with thyroid cancer were selected as case group and One-hundred and thirty people as control group. Risk factors in both groups were collected and compared. Based on interviews and questionnaires, we investigated the role in thyroid cancer of reproductive history and exogenous hormone use, goitre history, and food items rich in iodine – such as seafood – and vegetables containing goitrogens such as cruciferous vegetables. Thyroid diseases, cancer history in first degree relatives, and sociodemographic factors, were also investigated.

Results: The most common histological type was papillary carcinoma (65.4%), with a high density in 30-49 years old group. Most of thyroid cancer population was concerned by a familial history of thyroid cancer (65.4%). Sociodemographic factors show that education level and job were significant factors (p=0.001). Reproductive history (p=0.001), and fish consumption show that thyroid cancer patients had a lower consumption of sea products (p=0.0002) and a higher consumption of goitrogenic vegetables (OR=4.48; 95% CI= [2.21-9.10]; p=0.000].

Conclusions: Statistical analysis provides evidence that the number of pregnancies and food diets related to iodine may be related to the high incidence of thyroid carcinoma and contribute as risk factors for women in this region.

KEYWORDS: Thyroid-cancer, Case-control studies, Pregnancies, Iodine deficiency, Western Algeria

INTRODUCTION

Thyroid cancer (TC) incidence is on the rise worldwide¹. In Algeria, it is the third most common cancer in women, after breast cancer, and colorectum cancer².

Tumours of the thyroid gland are generally due to environmental and physiological interactions, childhood radiation exposure (including ionizing radiation)^{3,4} and iodine deficiency in iodine-deficient geographical areas. Moreover, dietary deficiency⁵ has also been implicated as a risk factor. Most thyroid disorders are more frequent in women than in men⁶, and in most populations, thyroid cancer incidence is three times higher during the period between puberty and menopause⁷, suggesting that female hormones may be related to thyroid carcinogenesis.

Several epidemiological studies have been conducted to investigate thyroid cancer risk about menstrual, reproductive history, and sociodemographic factors in Europe⁸⁻¹¹, Asia¹²⁻¹⁴, and the United States^{15,16}, but none in North Africa and Algeria.

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This study aims on gender differences and female reproductive history that may be involved in thyroid carcinogenesis during different ages in a population of the Western region of Algeria. We also focused on the frequency of food consumption known as goitrogenic foods like cruciferous vegetables, and seafood (rich in iodine) consumption, in order to determine a possible interaction between diet and thyroid cancer.

PATIENTS AND METHODS

Study Population and Data Collection

CASES DATA

We included all incident cases of histologically confirmed thyroid cancer diagnosed in the Hospital Center of Tlemcen (Algeria) between March 1, 2016, and May 30, 2016 among women that were aged between 15–80 years old at diagnosis.

The study was restricted to Algerian women, recruited from Western Algeria (North and South), speaking Arabic and French. We identified 53 patients meeting these criteria, and their attending physicians guaranteed permission for the interview process.

We used a detailed exposure history regarding reproductive events and oral contraceptive use. Therefore, only living cases were eligible for inclusion. The average time between the case diagnosis and the interview was 2.5 years.

CONTROLS DATA

Controls were randomly selected in the Hospital Center of Tlemcen (Algeria). We identified 130 eligible females controls, who accepted to be interviewed.

To be included in the study, participants must have been living in Algeria for at least 5 years at the year of reference and have no history of malignant thyroid nodules or any other personal history of cancer. The middle age has been set between 15 and 80 years old at the time of the interview, and the participants were not expected to take part in any other ongoing study or clinical trials.

After obtaining informed consent, the interviewers elicited information on sociodemographic characteristics, diet, alcohol consumption, tobacco smoking, anthropometric factors, hormonal and reproductive factors, previous medical conditions, residential history, and family history of cancer or benign thyroid conditions.

STUDY DESIGN

The food survey consisted of a weekly recall, a retrospective method by asking people about their food and drink consumption during the previous 7-days. The 7-days recall was conducted during an interview in which the interviewer asked the participant about the different cruciferous foods (brussels sprouts, cauliflower, artichokes, turnips, radishes), and seafood products consumed¹⁷.

Summary items for total cruciferous and other vegetable intake were obtained by summing up the frequency of consumption of each separate item in cruciferous group of vegetables cited before.

The level of consumption was divided into "low level consumption" indicating two times consuming or less in the week, and "high level consumption" meaning three times and more a week.

The seasonality and the region were taken into account for evaluation, and the answers were all reviewed and completed in order to minimize measurement error.

This work had been approved by the Scientific Committee of the University of Tlemcen and by the Ethics and Deontology Committee of the University of Tlemcen (CEDUT).

Statistical Analysis

Statistical analysis of data was performed using IBM SPSS Statistics ver. 25.0 for Windows (SPSS Corp., Armonk, NY, USA). A Binary Logistic Regression study was performed to determine a predictive model for female thyroid cancer, using the measured factors. *p*-value less than 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

The clinical characteristics of women with thyroid cancer (Table 1) show that the most common histological type remains papillary carcinoma (65.4%), followed by follicular carcinoma (21.2%), and finally mixed carcinomas (13.5%).

The diagnosis circumstances vary significantly from case to case, and the family background of thyroid carcinoma was present among over half of the patients (65.4%).

	Thyroid Cancer Population n= 53 (100%)
Age, years at diagnosis	
≤30	4 (7.7%)
[30-49]	31 (59.6%)
≥50	17 (32.7%)
Histology	
Papillary carcinoma	34 (65.4%)
Follicular carcinoma	11 (21.2%)
Mixed Follicular-papillary	7 (13.5%)
Diagnosis circumstances	
Incidental finding	13 (25%)
Dysphagia	5 (9.5%)
Pain in neck and throat	5 (9.5 %)
Swollen lymph nodes	14 (26.9%)
Other	15 (28.8%)
Family history of thyroid carci	noma
No	18 (34.6%)
Yes	34 (65.4%)

TABLE 1. Clinical characteristics of female thyroid cancer.

n, number of participants; %, percentage.

Characteristics of cases and controls

The sociodemographic characteristics of the cases and controls are shown in Table 2.

Age distribution was similar for the two groups (mean age was about 44.7 ± 12.37 years among cases and 44.02 ± 14.09 years in controls) and no statistically significant difference between cases and controls was observed. The proportion of women from Haut-Plains Areas (23.1%) and Coastal Areas (23.1%) is relevant among patients (1.5% in Haut-Plains, 5.4% in Coastal Areas). However, the Interior Region, including Tlemcen and its surroundings, remains the most dominant residence location with 53.8% among cases, compared to 93.1% among controls.

A significant difference (p=0,001) was reported between cases and controls regarding educational levels, with a higher percentage of illiteracy among cases (Cases =36.5% vs. Controls= 10.8%), and a higher percentage of graduate education among controls (Cases= 17.3% vs. Controls = 44.6%), and also regarding job (61.5%) among controls that were employees, and only (23.1%) of cases (p=0.001).

A tendency of overweighting is noted in both cases and controls, but there are no notable differences in smoking status in both populations.

Goitre and another medical history

Women who developed thyroid cancer were more likely to have health issues background with (34.6%) compared to (28.5%) of controls, but no

significant difference was observed concerning goitre history with only (11.5%) of women with thyroid cancer.

Menstrual factors and reproductive history

No significant differences have been observed in Marital and Menopausal Status, since most of women are Married (Cases =86.5% vs. Controls= 84.6%) and Menopausal (Cases =67.3% vs. Controls= 71.5%).

Reproductive history is about the number of children each woman has had and its impact on the mother's health. Nulliparous women are more frequent in cases than in control (p=0.09), but reproductive history shows significant differences concerning Multiparous women and especially women who had more than six pregnancies (p=0.001).

Miscarriages are rarely observed but almost present in Cases and absent in Controls (OR=2.43, 95% CI= [0.58-10.1]; p=0.22)

Exogenous hormone use

Oral contraceptives are generally taken by childbearing women, aged between 30 and 49 years old (Table 3). This medication intake concerns 61.5% of women with thyroid cancer, and 57.7% of controls (OR=1.17; 95% CI= [0.06-2.26], p=0.63) (Table 4).

More than 80% of the study population declared using combined oestrogen-progestin contraception when other patients in both Cases and Controls had inaccurate and unclear answers about their oral contraception generation pills. Therefore, that information was not taken into account in the present study.

Menopause treatments, known as hormone replacement therapy, concern only (1.6%) of controls. Thyroid cancer was not associated with the use of other exogenous hormone therapy, other than levothyroxine for thyroid issues.

Diet

The values found for seafood and fish consumption (Table 5) indicate significant differences (OR=0.21, 95% CI= [0.10 -0.42], p=0.00). Most of the patients with thyroid cancer declared that they rarely used to consume fish and seafood (69.2%). In contrast, we find contradictory results for the controls, since more than half of the population declared that they consume fish and seafood, once to twice a week (67.7%).

TABLE 2. Odds Ratios (OR) of thyroid cancer and corresponding 95% CI according to socio-demographic characteristics and lifestyle habits of cases and controls.

	Cases n= 52 (100%)	Controls n=130 (100%)	OR ^a	95% CI	p-value
Age. Years					
<30	6	20			
20.10	(11.5 %)	(15.4 %)			
30-49	29	72			
50-69	(55.8%)	(55.4%)			
50-09	(30.8%)	(23.1%)			
>70	1	7			
	(1.9%)	(5.4%)			
MEAN (SD)	44.7 ±12.37	44.02±14.05	1	[0.98-1.03]	0.73
Residence area		_			
Coastal areas	12	7			
Inland areas	(23.1%)	(5.4%) 121			
initiality areas	(53.8%)	(93.1%)			
Hautes Plaines areas	12	2			
	(23.1%)	(1.5%)			
			1.24	[0.58-2.65]	0.58
Education level	10	14			0.001
Initerate	(36,5%)	14 (10 8%)			0.001
Primary school	(30.370)	21			0.33
i illinai y benoor	(11.5%)	(16.2%)			0.00
Middle school	8	22			0.13
TT' 1 1 1	(15.4%)	(16.9%)			0.005
High school	10	15 (11 5 9/)			0.005
College	(19.270)	(11.370)			0.001
conege	(17.3%)	(44.6%)			0.001
			0.66	[0.53-0.82]	0.001
Job					
Homemaker	40	50			
Employee	(76.9%)	(38.5%)			
Employee	(23.1%)	(61.5%)			
	(2011/0)	(011070)	0.18	[0.09-0.39]	0.001
Body Mass Index (Kg/m ²)					
<18.5	3	8			
[10, 5, 0,5]	(5.8%)	(6.2%)			
[18.5-25]	(21, 29/)	38			
[25-30]	(21.270) 19	(29.270) 44			
	(36.5%)	(33.8%)			
>30	19	40			
	(36.5%)	(30.8%)			0.00
D 1 0 11			1.2	[0.83-1./]	0.33
Passive Smoking	13	102			
INCVCI	43 (82.7%)	(78.5%)			
Current	9	28			
	(17.3%)	(21.5%)			
			0.76	[0.33-1.75]	0.52

*Key: n, number of participants; %, percentage. OR: odds ratio, CI: confidence interval (p, level of significance <0.05).

Concerning cruciferous vegetable consumption, very significant results have been found (OR=4.48, 95% CI= [2.21-9.10], p=0.000) since thyroid cancer

patients declared to have a diet rich in cruciferous plants (73.1%), *vs.* only (37.7%) of controls, that declared to consume them every day.

	OC* Cases n= 52 (100%)	Controls n=130 (100%)	p-value
<29	5	3	0.23
	(9.6%)	(2.3%)	
30-49	17	50	
	(32.7%)	(38.4%)	0.63
>50	11	21	
	(21.1%)	(16.15%)	0.22

TABLE 3. Exogenous	hormone use matched	with year's g	roups (oral	contraceptives).
0				1 /

*n, number of participants; %, percentage. OR: odds ratio, CI: confidence interval (p, level of significance <0.05). *OC: oral contraceptives.

DISCUSSION

This study provides evidence that chronic diseases and history of goitre and high parity are related to thyroid cancer, especially in women of reproductive age (67.3% among thyroid cancer patients)

The incidence of thyroid cancers in Algeria has been increasing exponentially over the past 10 years particularly among women, who account for (11.7%) of all female cancers¹⁸.

Because of this high incidence, the identification of highly prevalent risk factors of women of reproductive age is of particular interest.

Clinical characteristics

The most frequent histological type in our study is papillary carcinoma and vesicular carcinoma, corresponding to the observations of various studies^{19,20}, including recent review²¹.

Recent data suggest that some variants of Papillary thyroid carcinoma are often more aggressive with a higher rate of metastases, and resistance to radioactive Iodine (RAI) therapy, and compromised survival. This mechanism of tumour resistance remains enigmatic. Genetic and epigenetic events appear to activate pro-proliferation pathways or inhibiting pathways that will enhance cell death, as well as loss or gain of cell surface receptors that will disturb the action of pharmacological agents (as BRAFV600E mutation)²¹⁻²⁴.

Despite those events, papillary thyroid carcinoma is generally associated with 10 years survival of over 95%²⁵.

BMI

Obesity and overweight are associated with various cancers, including thyroid tumours^{26,27}, but in our study, the results show that overweight affects both the patient and control populations, as well as moderate and morbid obesity.

The link between BMI and thyroid cancer remains a subjective factor in different studies. Some researchers hypothesize that it may be correlated with the presence of other diseases, such as diabetes, and physical activity²⁸, while others refute this link²⁹. Further research has also suggested that people who are overweight and obese get seek more often, which may lead to confusion about the influence of this factor^{30,31}.

Passive smoking

Tobacco consumption, as well as consumption of alcohol among women, are very rare, especially for regional culture since they are prohibited in the Muslim religion, which is dominant in the entire population. However, it is noted that exposition to cigarette smoke is present.

Tobacco is a significant risk factor in many cancers^{32,33} but it has also been a subject of debate in healthy subjects, as two studies show that it leads to an increase in basal metabolic rate and T3 and T4 thyroid hormones^{34,35}.

Education level and job

Our study showed that illiteracy had a significant impact on the patient population, affecting 36.5% of patients compared to only (10.8%) of controls (p<0.001).

On the other hand, we note that the control population has a higher university level than the controls (Controls=17.3%, Cases=44.6%, p<0.001).

Therefore, the observations made regarding the percentage of housewives is much higher in patients compared to controls (Cases=76.9% vs. Controls=38.5%).

TABLE 4. Odds Ratios (ORs) of thyroid cancer and corresponding 95% Confidence Intervals (CI) according to reproductive factors.

	Cases n= 52 (100%)	Controls n=130 (100%)	OR ^a	95% CI	p-value
Marital status Single Married	4 (7.7%) 45 (86.5%)	18 (13.8%) 110 (84.6%)	2.04	[0.94-4.45]	0.73
Veuve	(1.9%) 2 (3.8%)	(0.8%) 1 (0.8%)			
<i>Menopausal status</i> No Yes	35 (67.3%) 17	93 (71.5%) 37	1.22	[0.61-2.44]	0.57
<i>Childbearing</i> No	(32.7%) 17 (32.7%)	(28.5%) 37 (28.5%)	0.81	[0.41-1.64]	0.57
Yes Reproductive history	35 (67.3%)	93 (71.5%)	1.33	[1.12-1.57]	0.001
0 1	8 (4.4%) 4	35 (19.2%) 15	0.3	[0.1-0.7]	0.06
2	(2.2%) 7 (3.8%)	(8.2%) 23 (12.6%)	0.3 0.4	[0.1-1.2] [0.1-1]	0.09 0.05
3 ≥4	9 (4.9%) 24	28 (15.4%) 29	0.4	[0.1-1]	0.04
- Miscarriage	(13.2%)	(15.9%)	1.3 2.43	[1.1-1.6]	0.01 0.22
0 1 >2	50 (96.2%) 1 (1.9%) 1	128 (98.5%) 2 (1.5%) 0			
 Full-term pregnancies	(1.9%)	(0.0%)	1.3	[1.04-1.53]	0.02
0	9 (17.3%) 5 (9.6%)	36 (27.7%) 15 (11.5%) 22			
2 ≥3	(11.5%) 32 (61.5%)	(16.9%) 57 (43.7%)			
Oral Contraceptives No Yes	20 (38.5%) 32 (61.5%)	55 (42.3%) 75 (57.7%)	1.17	[0.06-2.26]	0.63
<i>Menopause Treatments</i> No Yes	52 (100%) 0 (0%)	126 (98.4%) 2 (1.6%)	0	0	0.99

Continued

TABLE 4 (CONTINUED). Odds Ratios (ORs) of thyroid cancer and corresponding 95% Confidence Intervals (CI) according to reproductive factors.

	Cases n= 52 (100%)	Controls n=130 (100%)	OR ^a	95% CI	p-value
Goitre history			0.64	[0.24-1.68]	0.36
No	46	108			
	(88.5%)	(83.1%)			
Yes	6	22			
	(11.5%)	(16.9%)			
Other hormone's history			1.26	[0.22-7.09]	0.79
No	50	126			
	(96.2%)	(96.9%)			
Yes	2	4			
	(3.8%)	(3.1%)			
Other Medical history			1.33	[0.67-2.64]	0.41
No	34	93			
	(65.4%)	(71.5%)			
Yes	18	37			
	(34.6%)	(28.5%)			
Diabetes type two			2.69	[0.82-8.78]	0.10
Yes	6	6			
	(3.3%)	(3.3%)			
No	46	124			
	(23.3%)	(68.1%)			
High blood pressure			1.50	[0.59-3.83]	0.39
Yes	8	11			
	(4.4%)	(7.7%)			
No	44	116			
	(24.2%)	(63.7%)			

*Key: n, number of participants; %, percentage. OR: odds ratio, CI: confidence interval (p, level of significance <0.05).

Another study carried out in the East region of Algeria (Setif city) shows a strong relationship between low education levels and a higher risk of breast cancer in women³⁶.

Those results contradict a Canadian study in which undergraduate education level was correlated with an increased risk of thyroid cancer compared to the population with a secondary level of education or less³⁷.

Family history

According to our results (Table 1) more than half of our population mentioned a family history of thyroid carcinomas. An Iranian study reported similar findings, with 77.5% of the population presented these data as an important risk factor $(p<0.01)^{38}$.

It should also be noted that the increased risk of cancer associated with a family history may reflect the existence of risk factors also related to the same exposure and lifestyle among family members³⁹⁻⁴¹.

Residence area

As for the geographical distribution of our population, most are located in Tlemcen (Algeria).

However, we noted that (23.1%) of patients came from highland, at the gateway to the Sahara, which can also be explained by the fact that Tlemcen, the chief town of the Wilaya, has the only care service in the north and south-west of the country. This difference can also be seen in the fact that the ethnicity of the populations in the north and south of the country differs. These ethnic differences have already been mentioned, especially between the different populations in the United States (African American, Hispanic, and Asian)⁴².

Other medical histories

We found in the literature that the risk of thyroid cancer is regularly associated with a history of goitre or the presence of thyroid nodules; in women, the relative risk is even more present (variation between 12 and 33.3 in case of nodule, and 5.6 to 6.6 in case of goitre)^{43,44}. **TABLE 5.** Odds Ratios (OR) and corresponding 95% Confidence Intervals (CI) according to cruciferous vegetables and sea food consumption's level.

	Cases (N= 52)	Controls (N=130)	OR	95% CI	p-value
Sea Food					
High level consumption	16 (30.8%)	88 (67.7%)			
Low level consumption	36 (69.2%)	42 (32.3%)			
			0.21	[0.20-0.40]	0.0002
Cruciferous Vegetables					
High level consumption	38 (73.1%)	49 (37.7%)			
Low level consumption	14 (26.9%)	81 (62.3%)			
			4.48	[2.21-9.10]	0.000

*Key: OR: odds ratio, CI: confidence interval, p-value significance <0.05.

However, other chronic diseases are present in our population. In Algeria, the prevalence of hypertension is 23.6% (23.1% in men and 24.1% in women)⁴⁵, and 10.5% of the population in 2016 was affected by Type 2 Diabetes mellitus⁴⁶. In our population, the presence of a medical history was found in both cases and controls. Although the literature shows few associations, between hypertension and thyroid cancer⁴⁷, the relative risk associated with diabetes is still present in separate meta-analyses^{48,49}.

Menstrual factors

Our results were supported by a study carried out in Morocco⁵⁰ where the average age was 44.06 ± 12.7 years, as well as from a study done in 2014 in USA, where the mean age at diagnosis was about 49 years for women. A percentage of 56.6% among thyroid women patients aged between 30 and 59 years, with a mean age of the population corresponding to 44.7 ± 12.4 years^{51,52}.

We noted that those results are close to the age of menopause, which concerns 32.7% of patients and 28.5% of controls. The hormonal changes observed during this period may be associated with complications, as two previous studies in Tunisia and the USA have shown^{53,54}. Therefore, this population should be closely monitored.

Reproductive history

Reproductive history defined by pregnancy number among cases is an important factor in many studies. We have noted that nulliparous women represent only a minority, unlike the controls (p=0.006).

Similar results were observed for a study in New Caledonia in women with thyroid cancer, where the number of pregnancies in women of childbearing age was a significant factor (OR=1.8), unlike postmenopausal women where no association was found (OR=0.8)⁵⁵.

We also noticed that the difference becomes highly significant as the number of pregnancies increases. This was also the case for different studies around the world^{55,56}. However, some other epidemiological studies have found that age at first birth and parity had no effect on the aetiology of papillary thyroid cancer⁵⁶⁻⁵⁹.

Other recent studies have also suggested that parity is an important risk factor in the first five years following pregnancy, but that this risk decreases over time^{56,60-62}.

No voluntary abortion has been reported in our study; however, no association could be made between miscarriages and the risk of developing thyroid cancer. Similar results have been reported in previous studies⁶³.

However, other studies have shown that for women with a history of hypothyroidism during pregnancy, the risk of miscarriage became higher (OR=2.73). This can be explained by the presence of autoimmune antibodies⁶⁴.

Exogenous hormone use

No significant association was found by the use of oral contraceptives, and given the Maghreb culture, oral contraceptives are only taken by married women. Despite this cultural influence, four other cohort studies⁶⁵⁻⁶⁹ and three other case-control studies⁶⁹⁻⁷¹ show the same results.

Several studies observed that female hormones, especially oestrogens, affect the proliferation of thyroid gland cells^{72,73}. In our study, hormone replacement therapy concerns only 1.6% of controls. Thus, no association was established with exogenous hormone therapies.

However, hormonal changes and fluctuations during the menstrual and reproductive cycles influence the secretion of thyroid hormones, and some studies showed an inverse association between artificial menopause and continuous use of contraceptives, and that hormones can have a protective effect against uncontrolled proliferation of thyroid cells^{74,75}.

Diet

The absorption of iodine by thyroid cells is achieved by a sodium iodide cotransporter that requires a mitochondrial energy supply. Therefore, the inhibition of mitochondrial oxidative phosphorylation led to a decrease in iodine uptake. Magnesium also plays a key role in preserving this mitochondrial homeostasis, as it is an enzyme cofactor, its deficiency led to decrease iodine uptake and so hormone synthesis. But mitochondrial dynamics can also be modified by thyroid tumour cells, in order to participate in the acquisition of migrating phenotype and gaining survival advantages [76]. Other studies also reported a possible correlation between increased mitochondrial fusion and chemoresistance in other cancers⁷⁷.

Iodine compounds are found exclusively in the marine flora and are usually released into the atmosphere and come back to the ocean continental regions through rain fall⁷⁸. Therefore, many areas in the world lack iodine in the natural food chain, and iodine supplementation became mandatory to prevent iodine deficiency disorders as behavioural and cognitive impairment, risk of early abortion, and risk of goitre development⁷⁹⁻⁸².

Most of thyroid cancers occurring worldwide are differentiated, including follicular and papillary cancers [83] which take roots in follicular cells of the gland. Studies show that regions with low dietary intake of iodine, increase follicular cancers⁸².

The present study shows a reverse association between seafood consumption and thyroid cancer, since the values found for seafood and fish consumption indicate significant differences (OR=0.21, 95%CI= [0.10 -0.42], p=0.00). Most of the patients with thyroid cancer (69.2%) declared they rarely consume fish and seafood, whereas we find contradictory results for the controls, since more than half of the population reported that they consume fish and seafood regularly (67.7%). Different case-control studies conducted in the USA, Europe and Asia found no significant association between thyroid cancer and fish and shellfish consumption, but these results were in-consistent across populations²².

Furthermore, our results show higher consumption of cruciferous vegetables (like brussels sprouts, turnips and cabbage) in patients compared to controls, suggesting a close relationship.

Many studies show that cruciferous plants contain a degraded form of thioglucosides, such as thiocyanates, which is a goitrogen substance, and may increase thyroid cancer risk by inhibiting iodine transport to the thyroid gland at low concentrations⁸⁴⁻⁸⁶.

But it is also well known that cabbage family vegetables provide at least 10% DRI for manganese, Vitamin B6 and folate, and approximately 50% of the DRIs (Dietary Recommended Intakes) in Vitamin C and K, in 100G⁸⁷, and they also have an anticancer activity due to their sulfuric compounds (such as glucosinolates) and polyphenols⁸⁸⁻⁹⁰.

However, optimal concentrations for a balanced diet are not quite clear till now, as well as nutritional recommendations for thyroid patients, since many studies have shown an impairment of thyroid gland function in severe species⁹¹⁻⁹³.

But other natural solutions can be found in plants since biological investigations leading to the antioxidant activity of compounds increased those last years. The potential of active ingredients derived from plants and food in inhibiting papillary thyroid carcinoma has been studied, and some plant-derived compounds (such as Curcumin)⁹⁴⁻⁹⁸, and also Tannins Saponins and Flavonoids⁹⁹, have proven their impact in preventing and treating thyroid cancer.

In the bioflavonoid family, Quercetin (3,30,40,5,7-pentahydroxyflavone) is an important compound found in more than twenty plants [100-102], with its anti-inflammatory, antihypertensive, anti-obesity, and finally, its potential as an anti-cancer agent including its role in cell cycle regulation and Tyrosine Kinase inhibition, as papillary and medullary thyroid cancers are mainly concerned by the prognostic role of Aurora Kinases^{103,104}.

In case the main limitation of using polyphenols in cancer therapies remains their low bioavailability, an interesting strategy has been suggested by using Hyaluronic acid as biological molecule that will achieve a targeted, and controlled release at the cancer tissue level^{105,106}.

Despite those results, it is important to underline that recall bias may occur in this type of case-control studies, when it comes to declarations made by cases that may over- or under-report

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their weekly consumption, or during the 24-hour recall survey. Indeed, it is important to emphasize that alternatives and more accurate methods for measuring iodine intake include the 24-h measurement of urinary iodine, in order to obtain a clear result. Although, this method remains more challenging to achieve in epidemiological studies, as the present study.

CONCLUSIONS

The present study shows the importance of fullterm pregnancies and the relationship that leads multiparous women to the risk of thyroid cancer. Goitre's background and family history are also important factors that should be taken into consideration. However, sociodemographic factors shed light on the importance of education level and jobless factors in patients with thyroid cancer. Further investigations should be undertaken to know menarche factors, duration of exogenous hormone use, and role of exposition to environmental factors in different ethnic groups of the region.

Considering our results about diet and lifestyle habits, the availability of food products, particularly seafood, for the various social classes of the population, especially in the Saharan and Mountainous regions, which are known to be prone to iodine deficiency, must be corrected in order to prevent risk factors for thyroid diseases.

Since the relationship between hormonal risk factors and thyroid cancer is not well understood, it is wiser to be alert to certain signs, and carefully monitor particular areas and groups of the population. Postmenopausal women should be firstly supervised in thyroid cell carcinogenesis process. Family screening for underlying thyroid diseases should also be systematic in people at higher risk, especially women with a hormonal background and multiple pregnancies.

HUMAN AND ANIMAL RIGHTS:

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

INFORMED CONSENT AND PATIENT DETAILS:

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

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CONFLICT OF INTEREST:

The authors declare that they have no competing interest.

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