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ORIGINAL ARTICLE

# Thyroid Carcinoma Pathological Features Following Salt Iodization in a Region of Former Iodine Deficiency and Endemic Goiter. A population-based study in Algeria, 1993-2013.

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## ABSTRACT

**Introduction.** The incidence of thyroid cancer (TC) has increased dramatically over the last three decades in Algeria, and the causes of this increase remain controversial. Until 1992, the country was iodine-deficient; however, little is known about the patterns and trends of TC pathological features following the introduction of iodized table salt to combat iodine deficiency and endemic goiter. **Methods.** Data on microscopically verified primary TC (C73) diagnosed between 1993 and 2013 were collected retrospectively using the independent case ascertainment method and the multisource approach to enhance data completeness. We used the European Network of Cancer Registries recommendations to determine the incidence date and the International Classification of Diseases for Oncology, 3rd edition, for TC morphological coding. We describe TC pathological patterns and trends over a 21-year period. **Results.** Between 1993 and 2013, 1,443 TC cases were diagnosed, of which 1,248 (86.5%) were in females (female-to-male sex ratio: 6.4:1). The mean age at diagnosis was 43.7 ± 14.8 years for females and 48.1 ± 15.3 years for males. Nodules were present in 90.1% of TC cases. The most frequent histologic types were papillary (PTC) (58.3%) and follicular (FTC) (29.7%). A significant increase in PTC and microcarcinoma, and a significant decrease in FTC and anaplastic histologic types, were observed over time. Capsular effraction and angioinvasion were observed in 29.2% and 23.9% of TC cases, respectively, and decreased significantly over time. **Discussion.** Algeria has a history of iodine deficiency and endemic goiter. The table salt iodization program introduced in Algeria in 1992 cannot solely explain the upward trends in TC incidence, which are mostly driven by the PTC histotype. Changes in medical practice, along with exposure to environmental factors, may also have played a role.

**Keywords:** Thyroid cancer, papillary, follicular, incidence, trends, iodine deficiency, iodized salt.

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## 1. INTRODUCTION

Since the early 1980s, the incidence of thyroid cancer (TC) has dramatically increased in many parts of the world [1], mainly driven by the papillary carcinoma subtype (PTC) and thyroid microcarcinoma (TMC). These upward trends in TC incidence were attributed to changes in medical practice [2,3], although a true increase due to exposure to known or still unknown risk factors has not been totally ruled out. Risk factors for TC include exposure to ionizing radiation (IR) [4], dietary iodine intake levels [5], genetic susceptibility [6], hormonal and reproductive factors in women [7], obesity [8], and exposure to endocrine disruptors [9]. In Algeria, TC is the third most common cancer in women (5.9%) [10]. In 2022, the standardized incidence rates (SIR) per 100,000 were 9.0 in women and 1.9 in men [10]. In 20 years, the incidence of TC has more than doubled, with nearly 75% of the increase attributed to PTC [11]. The annual percent change (APC) in TC incidence was +3.69%, +7.37% for PTC, and +13.10% for TMC [11]. During the same time period, the incidence of follicular thyroid carcinomas (FTC) significantly decreased (-3.78%) [11]. Until 1992, Algeria was iodine-deficient, leading the health authorities to implement the table salt iodization program nationwide in 1992 [12]. Using population-based data, we describe patterns and trends of TC pathological characteristics over a 21-year period in the wilaya of Oran, in the northwest of Algeria.

## 2. MATERIAL AND METHODS

We carried out a descriptive, retrospective, multicentric study using population-based data on primary TC cases diagnosed between January 1, 1993, and December 31, 2013, and collected in all healthcare facilities in the wilaya of Oran, in the northwest of Algeria, with a population of nearly 1,500,000 (4% of the Algerian resident population). We reviewed medical records and pathology reports of patients who underwent thyroid surgery between January 1st 1993 and December 31st 2013, in 43 healthcare facilities across Oran, including public and private clinics, and pathology laboratories. To achieve data completeness and validity, we used the multisource approach and the independent case ascertainment method as recommended by the European Network of Cancer Registries (ENCR) [13]: Only patients with histologically confirmed TC and who were residents of Oran at the time of their TC diagnosis were included in the study. We performed multiple crossovers between the different data sources to validate the histopathological diagnosis and the place of residence of each patient. Because pathologists do not report the patients' place of residence, TC cases that were identified through pathology reports only were cross-checked with electoral lists in the municipalities to confirm residency. Information of interest included age at TC diagnosis (or date of birth), sex, date of thyroid surgery, the presence of thyroid nodules (TN) and their number, tumor size, capsular effractions, angioinvasions, and histologic type. The incidence date was determined using the algorithm of the ENCR. Data were compiled in the same Excel file, and duplicates were excluded. For all TC patients included in the study, a pathologist conducted a central review of pathology reports in order to reascertain histological diagnosis.

**Case definition.**

The diagnosis of TC is anatomopathological, based on microscopic examination of the thyroid specimen. All TC cases (C73.9) [14] were subdivided into morphological subtypes, coded according to the International Classification of Diseases for Oncology, 3$^{rd}$ edition (ICD-O-3) [15], and grouped into 6 categories: PTC (ICD-O-3 codes: 8340, 8050, 8260, 8341-8344, 8350, 8450-8460); FTC (ICD-O-3 codes: 8190, 8290, 8330-8335); anaplastic thyroid carcinoma (ATC) (ICD-O-3 codes: 8012, 8020-8035, 8300); medullary thyroid carcinomas (MTC) (ICD-O-3 codes: 8345, 8346, 8347, 8510-8513); carcinomas with no other specification (carcinomas, NOS) (ICD-O-3 codes: 8000, 8010-8015, 8230,8337) ; and specified carcinomas but classified in the category "other carcinomas" (ICD-O-3: 8052, 8333, 8337, 8070, 8140, 9591, 8800). follicular variant of PTC (FVPTC) was grouped with PTC, and poorly differentiated TC with ATC.

**Inclusion criteria.**

Patients who have undergone thyroid surgery between 1993 and 2013 and whose microscopic examination of the thyroid specimen has revealed cancer. The incidence date was defined according to the ENCR algorithm [13]. Patients whose pathology reports were not retrieved.

**Exclusion criteria.**

Patients whose pathology reports were not retrieved.

**Statistical analysis.**

The variables included in the analysis were age at diagnosis (in years), as a continuous variable and in two categories (<45 years and ≥45 years), sex (women and men), incidence date, histologic type (PTC, FTC, ATC, MTC, other specified carcinomas, and carcinomas NOS), number of nodules (1 (solitary nodule) *versus* ≥2 (multiple nodules), TC size in millimeters, as a continuous variable and in categories (≤10 mm, 11-20 mm, 21-40 mm, >40 mm), and capsular effraction (yes/no) and angioinvasion (yes/no). Data were analyzed for the period 1993-2013 and for four calendar periods (1993-1997, 1998-2002, 2003-2007, 2008-2013) for

women and men separately. The chi-square test and Fisher's exact test were used for comparison of categorical variables. Analysis of variance was used for comparison of means. All statistical tests for heterogeneity and trends were two-sided, at the 5% significance level. SIR per 100,000 were computed for solitary and multiple thyroid nodules associated with TC and for solitary and multiple nodules associated with PTC. SIRs were computed by the direct standardization method using SEER*Stat software [16]. Annual percent change (APC) in incidence for the period 1993-2013 was estimated using the Joinpoint regression program (version 4.7.0.0), according to the method of Kim et al. [17].

**Ethical considerations.**

Throughout the study, the forms used to collect information on CT cases were stored in a cabinet to which only the principal investigator had the key. At the end of the data collection and validation process, the database was anonymized in order to protect patient privacy.

## 3. RESULTS

Demographic and clinical characteristics have been previously described [11]. Between 1993 and 2013, 1,443 TC cases were diagnosed among Oran residents, including 1,248 (86.5%) in women (female-to-male sex-ratio = 6.4:1). The mean age at diagnosis (±SD) was 43.7±14.8 years for women and 48.1±15.3 years for men (p<0.001).

**Tableau 1.** Pathological characteristics of thyroid carcinomas according to the period of diagnosis and sex, Oran, Algeria, 1993-2013.

| | Women | | | | | | Men | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total (n=1 248) n (%)** | **1993-1997 (n=96) n (%)** | **1998-2002 (n=255) n (%)** | **2003-2007 (n=297) n (%)** | **2008-2013 (n=600) n (%)** | ***P**** | **Total (n=195) n (%)** | **1993-1997 (n=13) n (%)** | **1998-2002 (n=44) n (%)** | **2003-2007 (n=47) n (%)** | **2008-2013 (n=91) n (%)** | ***P**** |
| **Nodules** | (n=980) | (n=74) | (n=167) | (n=252) | (n = 487) | | (n=144) | (n=10) | (n=28) | (n=41) | (n=65) | |
| Yes | 916 (93.5) | 60 (81.1) | 153 (91.6) | 240 (95.2) | 463 (95.1) | | 130 (90.3) | 8 (80.0) | 27 (96.4) | 38 (92.7) | 57 (87.7) | |
| No | 64 (6.5) | 14 (18.9) | 14 (8.4) | 12 (4.8) | 24 (4.9) | *<0.001* | 14 (9.7) | 2 (20.0) | 1 (3.6) | 3 (7.3) | 8 (22.3) | *0.2* |
| **Number of nodules** | (n=741) | (n=46) | (n=104) | (n=203) | (n=388) | | (n=90) | (n=5) | (n=10) | (n=28) | (n=47) | |
| 1 | 463 (62.5) | 36 (78.3) | 75 (72.1) | 122 (60.1) | 230 (59.3) | | 62 (68.9) | 4 (80.0) | 8 (80.0) | 19 (67.9) | 31 (66.0) | |
| ≥ 2 | 278 (37.5) | 10 (21.7) | 29 (27.9) | 81 (39.9) | 158 (40.7) | *<0.01* | 28 (31.1) | 1 (20.0) | 2 (20.0) | 9 (32.1) | 16 (34.0) | *0.81* |
| **Tumor size (mm)** | | | | | | | | | | | | |
| **Mean ± SD** | 26.4±17.3 | 32.6±19.4 | 30.1±17.7 | 27.4±17.2 | 24.4±16.8 | *<0.01* | 29.7±19.1 | 8.5±2.1 | 27.1±18.1 | 31 (12-70) | 28.2±19.4 | *0.048* |
| **Median, (Min-Max)** | 20 (2-100) | 30.6 (3-80) | 30.0 (5-85) | 23.5 (2-90) | 20 (2-100) | | 25 (3-70) | (7-10) | 21 (10-65) | 31 (12-70) | 20 (3-70) | |
| ≤ 10 | 138 (21.3) | 2 (6.1) | 13 (15.7) | 32 (18.6) | 91 (25.2) | *0.014* | 13 (16.5) | 2 (66.7) | 3 (30.0) | 0 (0) | 8 (18.2) | *<0.01* |
| 11-20 | 193 (29.7) | 11 (33.3) | 15 (18.1) | 50 (29.1) | 117 (32.4) | *0.072* | 24 (30.4) | 0 (0) | 2 (20.0) | 7 (31.8) | 15 (34.1) | *0.74* |
| 21-40 | 227 (35.0) | 13 (39.4) | 39 (47.0) | 64 (37.2) | 111 (30.7) | *0.036* | 25 (31.6) | 1 (33.3) | 3 (30.0) | 8 (36.4) | 13 (29.5) | *0.81* |
| > 40 | 91 (14.0) | 7 (21.2) | 16 (19.3) | 26 (15.1) | 42 (11.6) | *0.15* | 17 (21.5) | 0 (0) | 2 (20.0) | 7 (31.8) | 8 (18.2) | *0,56* |
| **Capsular effraction** | (n=631) | (n=49) | (n=92) | (n=156) | (n=334) | | (n=83) | (n=8) | (n=6) | (n=23) | (n=46) | |
| Yes | 364 (57.7) | 27 (55.1) | 65 (70.7) | 118 (75.6) | 154 (46.1) | *<0.001* | 45 (54.2) | 7 (87.5) | 5 (83.3) | 15 (65.2) | 18 (39.1) | *0.012* |
| No | 267 (42.3) | 22 (44.9) | 27 (29.3) | 38 (24.4) | 180 (53.9) | | 38 (45.8) | 1 (12.5) | 1 (12.5) | 8 (34.8) | 28 (60.9) | |
| **Angioinvasion** | (n=563) | (n=42) | (n=80) | (n=150) | (n=2911) | | (n=73) | (n=5) | (n=8) | (n=20) | (n=40) | |
| Yes | 282 (50.1) | 21 (50.0) | 49 (61.2) | 107 (71.3) | 105 (36.1) | *<0.001* | 34 (46.6) | 4 (80.0) | 7 (87.5) | 10 (50.0) | 13 (32.5) | *<0.01* |
| No | 281 (49.9) | 21 (50.0) | 31 (38.8) | 43 (28.7) | 186 (63.9) | | 39 (53.4) | 1 (20.0) | 1 (12.5) | 10 (50.0) | 27 (67.5) | |
| **Histologic subtypes** | (n=1 248) | (n=96) | (n=255) | (n=297) | (n=600) | | (n=195) | (n=13) | (n=44) | (n=47) | (n=91) | |
| Papillary carcinomas† | 742 (59.5) | 41 (42.7) | 107 (42.0) | 175 (58.9) | 419 (69.8) | *<0.001* | 101 (51.8) | 3 (23.1) | 12 (27.3) | 25 (53.2) | 61 (67.0) | *<0.001* |
| Follicular carcinomas | 379 (30.4) | 41 (42.7) | 115 (45.1) | 93 (31.3) | 130 (21.7) | *<0.001* | 50 (25.6) | 6 (46.1) | 16 (36.3) | 10 (21.3) | 18 (19.8) | *0.046* |
| Carcinomas NOS | 64 (5.1) | 9 (9.4) | 14 (5.5) | 14 (4.7) | 27 (4.5) | *0.26* | 19 (9.7) | 3 (23.1) | 6 (13.6) | 5 (10.6) | 5 (5.5) | *0.096* |
| Anaplastic carcinomas‡ | 20 (1.6) | 2 (2.1) | 7 (2.7) | 4 (1.3) | 7 (1.2) | *0.016* | 10 (5,1) | 0 (0) | 5 (11.4) | 4 (8.5) | 1 (1.1) | *0.027* |
| Medullary carcinomas § | 10 (0.8) | 0 (0) | 2 (0.8) | 2 (0.7) | 6 (1.0) | *NA* | 2 (1,0) | 0 (0) | 0 (0) | 0 (0) | 2 (2.2) | *NA* |
| Other¶ | 33 (2.6) | 3 (3.1) | 10 (3.9) | 9 (3.0) | 11 (1.8) | *<0.001* | 13 (6,7) | 1 (7.7) | 5 (11.4) | 3 (6.4) | 4 (4.4) | *<0.001* |

*Abbreviations : n, number ; p, test for statistical significance ; mm : millimeters ; SD, standard deviation ; Min ; minimum value ; max, maximum value ; NOS, no other specification ; NA, non applicable *p for trend ; † inclue follicular variant of papillary thyroid carcinomas ; § inclue poorly differentiated thyroid carcinomas ; ¶includs all other soecified carcinomas.*

Table 1 displays TC characteristics overall and for four calendar periods. In women, thyroid nodules were present in 93.5% of TC cases, of which 62.5% were solitary nodules. Over the study period, TC associated with nodules increased significantly, from 81.1% in 1993-1997 to 95.1% in 2008-2013; p<0.001. For thyroid solitary nodules, the APC was +4.6% (95% CI, 2.2%-7.1% ; p<0.001) and +6.2% (95% CI, 4.7%-9.0% ; p<0.001) for thyroid solitary nodules associated with PTC in women, while in men, the APC was +8.0% (95% CI, 1.0%-15.5% ; p=0.02) for thyroid solitary nodules and +16.2% (95% CI, 5.6-33.9; p=0.004) for solitary nodules associated with PTC (figure 1).

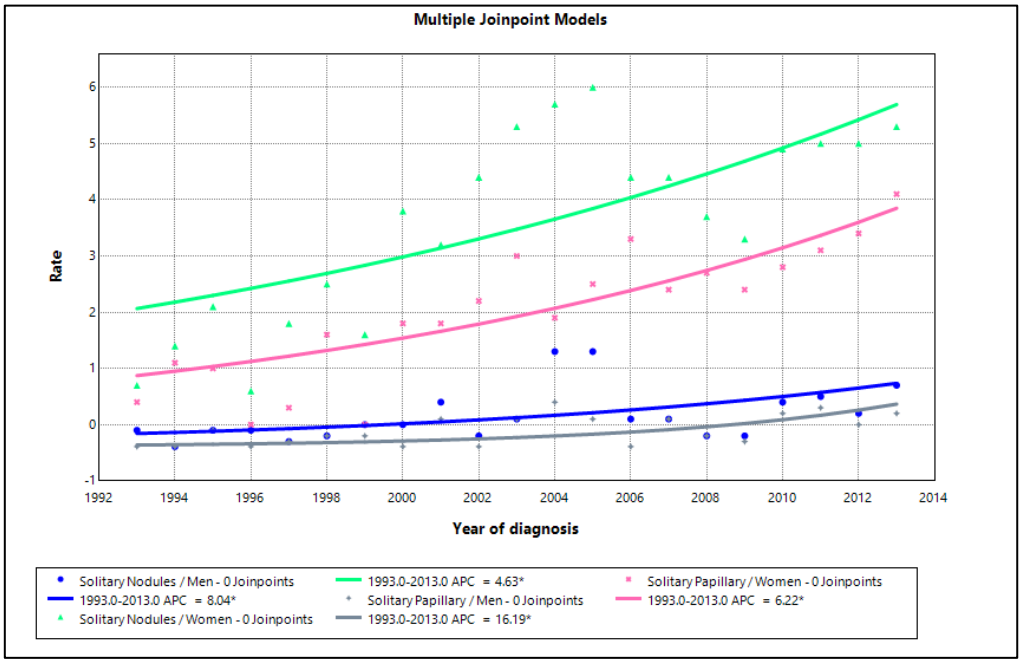


**Figure 1.** Annual percent change in the incidence of thyroid solitary nodules associated with TC stratified on sex, overall, and for the papillary subtype, Oran, Algeria, 1993-2013.

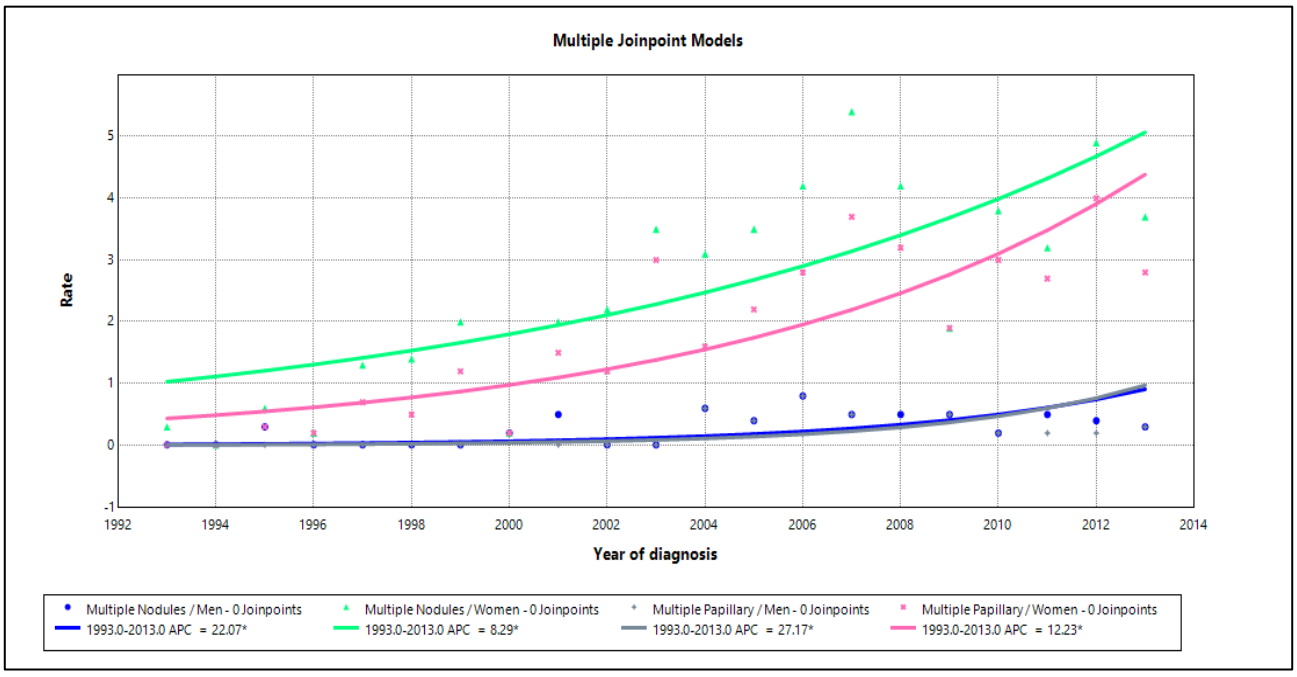


**Figure 2**. Annual percent change in the incidence of multiple thyroid nodules according to sex, overall, and for the papillary subtype, Oran, Algeria, 1993-2013.

When TC associated with multiple nodules was taken into account in the analysis, in women, the APC was +8.3% (95% CI, 3.1%-13.8%; p=0.03) and +12.2% (95% CI, 5.9%-18.9%; p<0.001) for thyroid multiple nodules associated with PTC, while in men, the APC was +22.1% (95% CI, 9.2%-41.8%; p=0.01) and +27.2% (95% CI, 15.0%-40.6%; p<0.001) for thyroid multiple nodules associated with PTC (figure 2).

In women, TC mean size was 26.4±17.3 mm. TMC and TC ≥ 20 mm represented 21.3% and 51.0% of cases, respectively. During the study period, TC size decreased significantly, from 32.6±19.4 mm in 1993-1997 to 24.4±16.8 mm in 2008-2013; p<0.01, with a significant increase in thyroid microcarcinoma (TMC) cases (6.1% in 1993-1997 to 25.2% in 2008-2013; p=0.014) and a non-significant decrease in TC >40 mm (21.2% in 1993-1997 to 11.6% in 2008-2013; p=0.15). Capsular effraction and angioinvasion were present in 57.7% and 50.1% of TC casesand significantly decreased from 2008 onwards.

PTC and FTC were the predominant histologic types (59.5% and 30.4%, respectively), with similar distributions in 1993-1997. However, from 2003 onwards, FTC and ATC significantly decreased (45.1% in 1998-2002 to 21.7% in 1998-2013; p<0.001 and 2.7% in 1998-2002 to 1.2% in 2008-2013, respectively; p=0.016). During the same time period, PTC significantly increased. In 2008-2013, PTC and FTC represented 69.8% and 21.7% of TC cases, respectively.

In men, TC associated with nodules rose from 80.0% in 1993-1997 to 87.7% in 2008-2013. TC mean size was 29.7±19.1 mm and significantly decreased over time (p=0.048), with TMC representing 15.9% and TC >40 mm, 21.5%.

Overall, PTC and FTC accounted for 51.8% and 25.6%, respectively;however, during the studied period, the incidence of PTC has nearly tripled (from 23.1% to 67.0%; p<0.001), while that of FTC, ATC, and other specified carcinomas significantly decreased.

**Tableau 2**. Pathologic characteristics of thyroid carcinomas in women according to age at diagnosis, Oran, Algeria, 1993-2013

| | < 45 (n=714) | | | | | | ≥ 45 (n=534) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total (714)** | **1993-1997 (n=65)** | **1998-2002 (n=142)** | **2003-2007 (n=163)** | **2008-2013 (n=344)** | ***P**** | **Total (n=534)** | **1993-1997 (n=31)** | **1998-2002 (n=113)** | **2003-2007 (n=134)** | **2008-2013 (n=256)** | ***P**** |
| **Tumor size (mm)** | | | | | | | | | | | | |
| **Mean ± SD** | 25.9±17.0 | 30.6±15.8 | 30.7±25.4 | 26.5±16.8 | 24.8±16.8 | *0.01*† | 27.1±17.7 | 38.3±25.9 | 29.4±15.9 | 29.4±17.5 | 24.5±16.8 | *0.048*† |
| **Mediane (Min-Max)** | 20 (2-100) | 30 (10-70) | 30 (5-85) | 20 (2-85) | 20 (2-100) | | 22 (2-80) | 20 (3-80) | 25 (5-75) | 30 (5-76) | 20 (2-80) | |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | |
| **Tumor size** | (n=381) | (n=24) | (n=48) | (n=91) | (n=220) | *0,09*‡ | (n=268) | (n=9) | (n=37) | (n=81) | (n=141) | *0.11*‡ |
| ≤ 10 | 81 (21.2) | 1 (4.2) | 7 (14.6) | 18 (19.8) | 55 (25.0) | *0.042* | 57 (21.3) | 1 (11.1) | 6 (16.2) | 14 (17.3) | 36 (25.5) | *0.48* |
| 11-20 | 116 (30.4) | 8 (33.3) | 8 (16.7) | 31 (34.1) | 69 (31.4) | *0.25* | 77 (28.7) | 3 (33.3) | 7 (18.9) | 19 (23.5) | 48 (34.0) | *0.11* |
| 21-40 | 139 (36.5) | 11 (45.8) | 23 (47.9) | 30 (33.0) | 75 (34.1) | *0.11* | 88 (32.8) | 2 (22.2) | 16 (43.2) | 34 (41.9) | 36 (25.5) | *0.041* |
| > 40 | 45 (11.8) | 4 (16.7) | 8 (16.7) | 12 (13.2) | 21 (9.5) | *0.3* | 46 (17.2) | 3 (33.3) | 8 (21.6) | 14 (17.3) | 21 (14.9) | *0.43* |
| **Capsular effraction** | (n=376) | (n=37) | (n=57) | (n=78) | (n=204) | | (n=255) | (n=12) | (n=35) | (n=78) | (n=130) | |
| Yes | 207 (55.0) | 19 (51.3) | 44 (77.2) | 55 (70.5) | 89 (43.6) | | 157 (61,6) | 8 (66.7) | 21 (60.0) | 63 (80.8) | 65 (50.0) | |
| No | 169 (45.0) | 18 (48.7) | 13 (22.8) | 23 (29.5) | 115 (56.4) | *<0.001* | 98 (38.4) | 4 (33.3) | 14 (40.0) | 15 (19.2) | 65 (50.0) | *<0.001* |
| **Angioinvasion** | (n=337) | (n=31) | (n=50) | (n=80) | (n=176) | | (n=226) | (n=11) | (n=30) | (n=70) | (n=115) | |
| Oui | 164 (48.7) | 15 (48.4) | 36 (72.0) | 55 (68.8) | 58 (32.9) | | 118 (52.2) | 6 (54.5) | 13 (43.3) | 52 (74.3) | 47 (40.9) | |
| No | 173 (51.3) | 16 (51.6) | 14 (28.0) | 25 (31.2) | 118 (67.1) | *<0.001* | 108 (47.8) | 5 (45.5) | 17 (56.7) | 18 (25.7) | 68 (59.1) | *<0.001* |

*Abbreviations : n, number ; mm, millimeters ; SD standard deviation ; Min, minimum value ; Max, maximum value ; *p for trend ; †analysis of variance ; ‡p for heterogeneity*

Table 2 displays TC pathologic characteristics in women, stratified by age. A significant decrease in TC size over time was observed, from 30.6±15.8 mm in 1993-1997 to 24.8±16.8 mm in 2008-2013 in women <45 years (p=0.01), and from 38.3±25.8 mm to 24.5±16.8 mm (p=0.048) in women ≥45 years. Meanwhile, TMC significantly increased, from 4.2% in 1993-1997 to 25.0% in 2008-2013 (p=0.042) in women <45 years, and from 11.1% in 1993-1997 to 25.5% in 2008-2013 (p=0.48), although the difference did not reach statistical significance. The frequency of TC > 40 mm was higher in women ≥ 45 years compared to women < 45 years (11.8% and 17.2%), with

a non-significant decrease over time in both age groups. Capsular effraction and angioinvasion were present in 61.6% and 55.0% (p=0.7), in women ≥45 years and in 52.2% and 48.7% (p=0.4) in women <45 years, and significantly decreased over time in both age groups (table 2).

In men, the TC mean size was 28.9±19.1 mm in <45-year-oldsand 30.5±19.3 mm in men ≥45-year-olds. Capsular effraction and angioinvasion were more frequent in ≥45-year-olds than in <45-year-olds (56.8% and 51.7%, respectively), and significantly decreased in <45-year-olds (p=0.02), while in ≥45-year-olds, the decreasing trend was only observed for angioinvasion (p=0.01). Age at TC diagnosis varied according to histologic type. PTC, FTC, and MTC were diagnosed during the fourth decade of life, and ATC in the fifth decade (p<0.001) (table 3). The female predominance observed in PTC and FTC was less pronounced in ATC (female-to-male sex ratio: 7.4:1, 7.5:1, and 2.3:1; p<0.001).

**Table 3.** Age at thyroid cancer diagnosis according to histologic subtype, Oran, Algeria. 1993-2013.

| | Mean age (±SD) | mediane [Q25-75] | min | max | n | *p* |
|---|---|---|---|---|---|---|
| **Histological subtypes** | | | | | | ***<0.001*** |
| Papillary | 43.3±14.7 | 42.0 [32.0-54.0] | 11.0 | 82.0 | 800 | |
| Follicular | 43.3±14.9 | 42.0 [32.0-54.0] | 12.0 | 81.0 | 402 | |
| Carcinoma, NOS | 51.7±16.1 | 53.0 [41.0-66.0] | 13.0 | 77.0 | 73 | |
| Anaplastic | 51.8±19.6 | 54.0 [36.0-66.5] | 15.0 | 94.0 | 55 | |
| Medullary | 47.7±19.4 | 41.0 [32.5-59.5] | 25.0 | 83.0 | 11 | |
| Others | 57.7±15.1 | 61.5 [50.2-67.8] | 24.0 | 80.0 | 18 | |

*Abbreviations : Q, quartile ; min, minimum ; max, maximum ; n, number ; NOS, no other specification ; p, test for statistical significance.*

PTC were significantly smaller (24.3±16.6 mm) compared to FTC (32.1±18.4 mm), ATC (33.8±11.7 mm), and MTC (32.5±14.4 mm); p<0.001. Multifocality was frequently observed in PTC (18.8%) compared to FTC (8.6%), while capsular effraction and angioinvasion were more frequently observed in FTC (80.0% and 89.5%) and ATC (72.3% and 76.5%); p<0.001.

## 4. DISCUSSION

The objectives of our study were to describe pathological characteristics of TC diagnosed in Oran residents over a 21-year period and to discuss the possible factors that may have caused the observed trends. Between 1993 and 2013, 1,443 primary TCs were diagnosed, including 1,248 (86.5%) in women. The female predominance observed in the cohort was more pronounced in patients <45 years compared to patients ≥45 years. PTC (58.4%) and FTC (28.3%) were the predominant histologic types. During the studied period, the incidence of PTC and TMC significantly increased, while that of FTC, ATC, and TC size significantly decreased. Capsular effraction and angioinvasion were more frequently observed in FTC and ATC and significantly decreased over time.

In most population-based cancer registries, PTC is the predominant histologic type (70% to 90%), while FTC represents 5% to 10% [18]. Higher incidence of FTC is common in iodine-deficient regions [19]. When iodized table salt is introduced, the PTC-to-FTC ratio increases with a 15- to 40-year latency [19]. For example, in Brazil, between 1997 and 2008, the PTC-to-FTC ratio increased from 2.6 to 8.5 in women and from 2.7 to 8.6 in men [20], whereas the PTC-to-FTC ratio slightly increased, from 9.1 to 11.7 in women and from 6.5 to 7.5 in men in the USA, mainly because iodized salt consumption has remained stable in the USA since 2000 [20]. In our study, the increased incidence of PTC and the downturn in the incidence of FTC from 1997 onwards may reflect the transition from iodine deficiency to adequate dietary iodine supplementation. Considering the 15- to 40-year latency period for the clinical expression of iodized salt introduction [19], the PTC-to-FTC ratio observed in our study in 1993-1997 could reflect the period of iodine deficiency, whereas that observed from 2003 onwards could reflect adequate iodine supplementation. Furthermore, capsular effraction and angioinvasion that were observed in 44.1% and 35.4% of TC cases have been linked to BRAF mutations frequently observed in goiter-endemic areas when dietary iodine supplementation is introduced [21].

FTC is observed around the age of 50 with a female-to-male sexr atio of 1.5:1 [21]. It usually presents as a solitary intrathyroid mass measuring more than 20 mm in diameter. Compared to other populations, FTC patients in our study were younger, with a female predominance. About 74% of FTC cases were associated with solitary nodules, 80.0% had capsular effraction, and 72.3% had angioinvasion.

ATC is rare (1% to 2%) and highly aggressive [21], with increased incidence in iodine-deficient areas and low socioeconomic status. In most regions of the world, the incidence of ATC had decreased due to the introduction of the iodized table salt program, better detection of differentiated TC, and the advent of immunohistochemistry that helped distinguish between ATC, MTC, and lymphomas [21]. ATC is rare before the age of 40 and occurs in less than 25% of cases before the age of 60 years, with a slight female predominance (female-to-male sex ratio = 1.5:1). Most ATC develop from pre-existing untreated or unrecognized PTC or on a goiter [21]. In our study, the mean age at ATC diagnosis was 51.7±19.6 years, and the female-to-male sex ratio was 2.3:1. ATC was diagnosed following self-neck check in 87% of cases, and in nearly 51% of cases, an unrecognized goiter was discovered during microscopic examination of the thyroidectomy specimen [11].

The MTC that represents 5%-10% of TC cases occurs in sporadic or hereditary forms [21]. The sporadic form represents 65% of MTC cases. MTC occurs around 50 years for sporadic forms and 30 years for hereditary forms. The female-to-male sexratio is close to 1, with a slight female predominance. In our cohort, the mean age at diagnosis was 47.7±19.4 years, with 50% of patients younger than 41 years at TC diagnosis. The female-to-male sex ratio was 5:1.

within the limits of a descriptive study, a few hypotheses can be discussed to explain variations of TC features over time. Exposure to IR is a clearly established and well-quantified risk factor for PTC. The risk of PTC has been attributed to exposure to IR delivered after nuclear tests or accidents [22], the use of IR for the treatment of benign medical conditions [23], dental radiographs [24], computed tomography (CT) imaging [25], the use of $^{131}$I for diagnostic and therapeutic purposes [26], and radiotherapy received for the treatment of head and neck cancers [27]. However, attributing variations observed over time in our study to IR exposure would be speculative, as we do not have data to support this hypothesis.

Dietary iodine levels influence the distribution of TC histologic types rather than its overall incidence, with a predominance of FTC in iodine-deficient regions [19]. When iodized table salt is introduced, the PTC-to-FTC ratio increases with a latency that may vary from 15 to 40 years [19]. Thus, the prevalence of FTC is often used to assess iodine deficiency [5, 19]. In our cohort, FTC represented 29.7% of all histologic types, whereas in developed countries, this frequency does not exceed 10% and has been attributed to dietary iodine supplementation introduced in the 1920s [5]. Algeria has a history of iodine deficiency and goiter endemicity [28]. Iodine status has been suspected to increase the risk of TC among women compared to men [5], potentially explaining the observed difference in incidence by sex in Oran. In addition, differences in risk according to histologic type have been associated with iodine intake [5]. In Africa, FTC predominates in regions with iodine deficiency and endemic goiter [28]. When dietary iodine is introduced in a population with a previous background of iodine deficiency, there is a shift towards an increase in the PTC-to-FTC ratio within 15-40 years, with no actual change in the overall TC incidence [5,19]. In 1992, the program of iodized table salt was introduced in Algeria. The increased PTC-to-FTC ratio observed in our study over time may reflect a shift from iodine-deficient to iodine-sufficient-to-excessive status. In 2006-2009, a case-control study assessed iodine status in a group of pregnant women in Oran and age-matched non-pregnant controls and found the urinary iodine concentration was in the optimal range [29]. In 2018, a cross-sectional study carried out in Oran, including 507 women aged ≥18 years, found that Oran has sufficient iodine levels, with a median urinary iodine concentration of 131.8 µg/l, and 83% of subjects with urinary iodine concentrations >100 µg/l. The proportion of households consuming iodized salt according to WHO standards (≥ 15 ppm) was 82% [30]. Considering the 15- to 40-year latency for the clinical expression of past phases of iodine nutrition [19], we assume that the low PTC-to-FTC ratio in the first period of the study (1993-1997) reflects the iodine-deficiency period, whereas the increased PTC-to-FTC ratio in the later period (2008-2013) reflects the late effects of iodine supplementation.

Among thyroid cancer patients, 90.9% had goiter or thyroid cold nodules, a characteristic commonly observed in populations with either deficient or excessive nutritional iodine intake. These benign thyroid conditions had led to thyroid surgery, with a systematic use of total and near-total thyroid surgery [31], which helped detect small carcinomas as shown in other populations [32].

Multinodular goiters (MNG) and thyroid cold nodules (TCN) have been associated with a higher incidence of PTC [33-35]. Both iodine deficiency and supplementation promote the development of benign thyroid conditions, leading to thyroid surgery and the diagnosis of PTC incidentalomas. The long latency in the correction of endemic goiter [19], when the dietary salt iodization program is introduced in a population, may explain the high prevalence of MNG in patients ≥45-year-olds in our cohort [31]. In Switzerland, for example, 30 years after iodized table salt was introduced, the prevalence of goiter was 75% in 50-60-year-olds [5].

The joint effect of exposure to IR and iodine deficiency on the rise of TC incidence has been suggested, with the risk of radiation-induced TC being 2 to 3 times higher in iodine-deficient areas [36]. Zablotska et al. examined 12,000 individuals in Belarus ≤18 years old at the time of the Chernobyl accident. After adjustment for IR doses, the prevalence rate of TC was significantly higher in individuals

who reported a history of nodules (OR: 23.21), diffuse goiter (OR: 5.15), and in individuals with diffuse or nodular goiter at screening (ORs: 19.79 and 3.16) [37].

The decline in the incidence of ATC observed in our study during the late study period is probably related, at least in part, to the correction of iodine deficiency, as suggested in Europe and South America [5,19].

Obesity has been associated with an increased risk of TC [8]. Insulin resistance, a typical feature of obesity, is reported in 50% of patients with PTC [37], and body mass index (BMI) is directly related to TC in women [38]. In our cohort, 21.3% of patients had a BMI > 33 kg/m². Obesity may explain the increased incidence of PTC, particularly in women. In 2010, the prevalence of obesity in adults aged 35-70 years was 9.1% (95% CI: 7.1%-11.0%) in men and 30.1% (95% CI: 27.8%-32.4%) in women [39]. The prevalence of diabetes has also increased in Oran, from 7.1% in 1998 to 10.5% in 2012 in individuals aged 18-70 years old [40].

To the best of our knowledge, our study is the first to describe trends of TC pathological features using many TC cases collected in an unselected and homogeneous population in the second largest wilaya in Algeria. We used the ENCR recommendations to achieve a high level of data completeness and validity across the studied period. Only TC cases with microscopic confirmation and validated place of residence were included in the study. Data collection processes also included a systematic recovery of demographics, pathological features, and tumor size. In 1988, the WHO updated the classification of morphologies and considered the PTCFV to be PTC. Since our study included patients diagnosed between 1993 and 2013, it is unlikely that this revision has influenced the observed trends for PTC, and it is noteworthy that the proportions of PTCFV were similar in the 4 time periods. Furthermore, information on TC histologic type was accurate and complete, as shown by the lower frequency of TC cases with poorly specified histology in later years. Despite our efforts to achieve a high level of data completeness and validity, we could not retrieve data on TC patients treated in medical centers outside the wilaya of Oran, but these patients represented less than 5% of the cohort. We also failed to find medical records and pathology reports of all TC patients diagnosed during the early period of the study, and information on tumor size, nodules, and other microscopic characteristics such as capsular effraction and angioinvasion was not complete. Also, there was a significant decrease in missing data over time that could explain part of the upward trends of some pathological features. However, it is unlikely that these limitations have invalidated our study, as the observed trends are consistent with the general context that includes a history of iodine deficiency and endemic goiter, the high frequency of nodules and goiter in previously asymptomatic patients, and the changes in medical practice that occurred during the studied period. Also, our results concerning trends by histology and tumor size align well with those of previously published studies.

Within 21 years, the incidence of TC has tripled in Oran. Striking observations include a rise in TC incidence mostly due to increased incidence of PTC, in particular PTC of small size in women and larger ones in men, with decreasing proportions of FTC. Increased diagnostic activity, improvements in education, and greater awareness of the disease in the general population, along with lifestyle and environmental factors, may have played a role. The increasing PTC-to-FTC ratio over the study period suggests that differences in iodine intake over time may have caused a shift from FTC to PTC predominance and that changes in medical practice, including the introduction of thyroid ultrasound, fine needle aspiration, and more detailed microscopic examination of the thyroid specimen by pathologists, may have caused the upward trends, although a true increase due to exposure to risk factors such as obesity and endocrine disruptors cannot be totally ruled out. Because of its relatively low incidence, assessing TC incidence trends over time requires long periods of observation, which increases the likelihood of confounding from other risk factors that may have changed over the same time period. Also, the latency period after exposure of susceptible individuals to iodine deficiency or supplementation and subsequent changes in the thyroid cancer incidence is not known, with experts suggesting it could be 15 to 40 years [19].

The understanding of TC etiology is still limited, and it is still difficult to identify the exact cause of the increasing TC trends in Oran. Future large-scale studies assessing risk factors and host susceptibility are needed to clarify the role of iodine supplementation programs, among other factors, on PTC and FTC patterns and trends and mechanisms that promote the development of TC and lead to population-based prevention programs.

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